

Anthony Di Battista, Manager
Regulatory Affairs and Toxic Substances Compliance
Toxicology, Regulatory Auditing & Compliance

8EHQ-U275-13321
ciba

Telephone: (914) 479-2776
Fax: (914) 479-4074

February 2, 1994

8EHQ-95-13321

8895000010

(A)

Ciba-Geigy Corporation
444 Saw Mill River Road
Ardsley, New York 10502-2699
Telephone 914 479-5000

EXPRESS MAIL
RETURN RECEIPT REQUESTED

SANITIZED COPY

Document Processing Center (7407)
(Attn.: Section 8(e) Coordinator)
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

COMPANY SANITIZED

RE.: TSCA Section 8(e) Notice: ZK RT 1507

Dear Section 8(e) Coordinator:

05 FEB - 8 AM 7:50

RECEIVED
CIBA-GEIGY

Ciba-Geigy Corporation (Ciba) requests that the specific chemical name and CAS Number shown in brackets in this letter be treated as Confidential Business Information. We enclose a sanitized copy of this letter for the public file. The enclosed report contains no CBI.

In accordance with EPA's March 16, 1978, policy statement on Section 8(e) reporting under the Toxic Substances Control Act and EPA's June 1991 TSCA Section 8(e) Reporting Guide, Ciba wishes to bring to your attention kidney, liver, and dental effects observed with ZK RT 1507 in a 28-day oral toxicity study in the rat. Chemically, ZK RT 1507 is []. ZK RT 1507 may be referred to generically in the public file as "triaryl sodium salt of antimony hexafluoride."

In a 28-day oral gavage study, with doses up to 250 mg/kg/day, male and female Wistar rats exposed to ZK RT 1507 exhibited kidney damage, liver effects, and abnormal growth conditions of the animals' incisors. The kidney effects, mainly microscopic degeneration of the tubules, were seen at all dose levels (5, 50, and 250 mg/kg/day), although some recovery and regeneration did occur in a post-recovery group held for an additional four-week period previously dosed at the 250 mg/kg/day level. Within the intermediate group (50 mg/kg/day), stomach irritation was seen in both males and females with an increased kidney weight occurring in the males.

In the 250 mg/kg dose group animals, numerous effects were evident. Even in the recovery group, both sexes developed incisors that were white in color, coated and partly broken off, and/or irregularly ground by the third week post exposure. Body weight gain and food consumption, especially in the males, were decreased but minimal for the females. Also, concerning the food consumption and weight gain, animals in the group were switched from normal pellet chow to a more chewable, pulverized, powder formula and the decrease in weight gain was reduced by the end of the study.

2/24/95

(b)

The clinical signs observed in the highest dose group reflected effects to the liver and kidneys. Although no evidence for pathologic effects was seen in the liver, the increases noted in the serum transaminases do indicate potential organ effects.

The kidney, however, showed both blood biochemical and pathologic manifestations. The pathologic findings included degeneration of the tubules with proteinaceous casts and an increased amount of hyaline resorption bodies and urothelial hyperplasia. The blood parameters showed an increase in creatinine and urea and decrease in glucose, total protein, albumin, and globulin. Also, all levels did return to normal in the recovery group except for one female who had developed a chronic interstitial nephritis. Animals in this group also encountered decreased red blood cell count, hemoglobin, hematocrit, and mean corpuscular volume (male only) and differential neutrophilic leucocyte counts. However, after a 4-week recovery period, all blood parameters returned to normal except the lymphocyte count. No mortality occurred in this study.

Based on the kidney degeneration occurring in all dose groups and the blood and liver effects occurring at the 250 mg/kg, as well as the unusual animal dental effects found in the recovery animals, Ciba considers the study to be TSCA 8(e) reportable. A copy of the final report (229 pages), entitled "Subacute 28-Day Oral Toxicity with TKK 30059 (ZK RT 1507) by Daily Gavage in the Rat, Followed by a 28-Day Recovery Period," is enclosed.

ZK RT 1507 is an imported chemical substance that is the subject of a recent Premanufacture Notification, P94-464. A Notice of Commencement has not yet been filed. The substance is used as a catalyst for homopolymerization of epoxy resins by heat cure.

In response to these findings, Ciba will do the following:

1. Modify the Material Safety Data Sheet to reflect these findings.
2. Notify persons working with this compound of the new findings in accordance with the notification requirements of OSHA's Hazard Communication Standard (29 CFR 1910.1200).

Please contact the undersigned if you need any additional information.

Very truly yours,

A. Di Battista

Anthony Di Battista

S M. 1.95

REPORT

CONTENTS NO 1001

SUBACUTE 28-DAY ORAL TOXICITY WITH
TKK 30059 (ZK RT 1507)
BY DAILY GAVAGE
IN THE RAT
FOLLOWED BY A 28-DAY RECOVERY PERIOD

NOTOX Project 126282
NOTOX Substance 43092

- page 1 of 229 -

05 FEB - 8 M 7:50

STATEMENT OF GLP COMPLIANCE

NOTOX B.V., 's-Hertogenbosch, The Netherlands

The study described in this report was conducted in compliance with the most recent edition of:

The OECD Principles of Good Laboratory Practice

which are essentially in conformity with:

The United States Food and Drug Administration. Title 21 Code of Federal Regulations Part 58.

The United States Environmental Protection Agency (FIFRA). Title 40 Code of Federal Regulations Part 160.

The United States Environmental Protection Agency (TSCA). Title 40 Code of Federal Regulations Part 792.

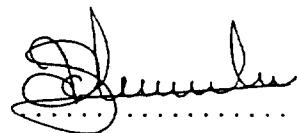
Japanese Ministry of Health and Welfare (Notification No. 313).

Japanese Ministry of Agriculture, Forestry and Fisheries 59 Nohsan Notification No. 3850, Agricultural Bureau, 10 August 1984.

Ministry of International Trade and Industry (MITI), GLP Standards applied to Industrial Chemicals, Japan.

Study Director:

Ir. A.C.M. Schoenmakers



Date: 03 January 1995

QUALITY ASSURANCE STATEMENT

NOTOX B.V., 's-Hertogenbosch, The Netherlands.

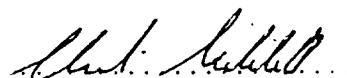
Study procedures were subject to periodic inspections and general non study specific processes were also inspected at periodic intervals.

This report was audited by the NOTOX Quality Assurance Unit and the methods and results accurately reflect the raw data.

DATES OF QAU INSPECTIONS/ AUDITS	REPORTING DATES
08 July 1994	08 July 1994
09 August 1994	09 August 1994
21 August 1994	22 August 1994
22 August 1994	22 August 1994
05 September 1994	05 September 1994
06 September 1994	06 September 1994
20 September 1994	20 September 1994
26 September 1994	26 September 1994
13 and 22 December 1994	22 December 1994

Quality Assurance Manager

C.J. Mitchell B.Sc.

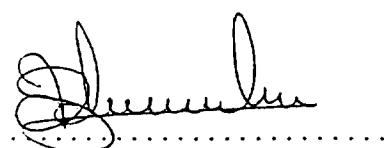


Date: 4-1-95

REPORT APPROVAL

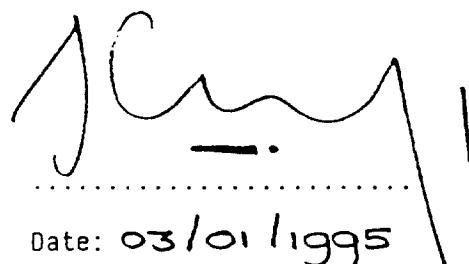
STUDY DIRECTOR :

Ir. A.C.M. Schoenmakers



Date: 03 January 1995

MANAGEMENT :

Dr. I.C. Enninga
Technical Director
.....|

Date: 03/01/1995

CONTENTS

SUMMARY	7
PREFACE	8
TEST SUBSTANCE	8
TEST SUBSTANCE FORMULATION	8
CHEMICAL ANALYSIS OF DOSE PREPARATION	9
PURPOSE AND RATIONALE	9
GUIDELINES	9
ARCHIVING	9
TEST SYSTEM	10
ALLOCATION	10
ANIMAL HUSBANDRY	10
DOSE LEVEL SELECTION	11
TREATMENT	11
OBSERVATIONS	11
CLINICAL LABORATORY INVESTIGATIONS	12
Haematology	12
Clinical Biochemistry	13
PATHOLOGY	14
Necropsy	14
Organ Weights	15
Histotechnology	15
Histopathology	15
STATISTICAL ANALYSIS	16
RESULTS	17
Analysis of Dose Preparations	17
Observations	17
Mortality	17
Clinical Signs	17
Body Weight	17
Food Consumption	18
Ophthalmoscopic examination	18

SUMMARY

Subacute 28-day oral toxicity with TKK 30059 (ZK RT 1507) by daily gavage in the rat followed by a 28-day recovery period.

Based on the results of a 5-day range finding study, the dose levels for the 28-day toxicity study were selected to be 0, 5, 50 and 250 mg/kg/day.

The study was based on the following guidelines:

- EEC Directive 92/69/EEC, B.7 Sub-acute Toxicity - Oral, 1992.
- OECD No. 407, Repeated Dose Oral Toxicity - Rodent, 1981.
- Substance Law 1987, Notification of Dec. 9 1986 by EA, MHW and MITI.

The test substance was administered daily for 28 days by oral gavage to SPF-bred Wistar rats. One control group and three treated groups were tested, each consisting of 5 males and 5 females. An extra 5 animals per sex in the control and high dose group were allowed 28 days of recovery.

The following parameters were evaluated:

clinical signs daily, body weight and food consumption weekly; ophthalmoscopy at weeks 4 and 8; clinical pathology and macroscopy at termination; organ weights and histopathology on a selection of tissues.

RESULTS

Accuracy, stability and homogeneity of test substance formulations were demonstrated by analyses.

5 mg/kg/day: 1) Degeneration of renal tubules in males at week 4.

50 mg/kg/day: 1) Degeneration of renal tubules in males at week 4.
2) Irritation of the stomach in males and females.
3) Kidney weight slightly increased in males.

250 mg/kg/day: 1) Hunched posture and piloerection in week 4 of recovery, together with broken and abnormal incisors.
2) In males, body weight gain and food consumption decreased during treatment, and slightly decreased during recovery. In females, body weight effect were minimal.
3) Anaemia in males and females at week 4, and increased neutrophils at weeks 4 and 8.
4) Increased creatinine, urea, liver enzymes, triglycerides and inorganic phosphate; decreased glucose, proteins and chloride levels at week 4. No significant effects at week 8.
5) Degeneration of renal tubules was seen in males and females at week 4. After recovery, regeneration/repair of the kidney occurred.
6) Irritation of the stomach at weeks 4 and 8.
7) Liver weights increased at week 4, kidney weight increased at weeks 4 and 8.

CONCLUSION

From the results presented in this report a definitive No Observed Effect Level (NOEL) could not be established as signs of renal toxicity were still present in animals of the lowest dose group (5 mg/kg/day).

CONTENTS (CONT'D)

RESULTS (CONT'D)	
Clinical Laboratory Investigations	19
Haematology	19
Clinical Biochemistry	19
Pathology	20
Macroscopic Examination	20
Organ Weights	20
Microscopic Examination	20
DISCUSSION AND CONCLUSION	21
FIGURES	23
Body Weights - males	24
- females	25
Body Weight Gain - males	26
- females	27
TABLES - SUMMARY DATA	28
Clinical Signs, Daily	29- 36
Body Weight	37- 40
Body Weight Gain	41- 44
Ophthalmoscopic examination	45- 46
Haematology	47- 50
Clinical Biochemistry	51- 58
Organ Weights / Organ-Body weight Ratios	59- 66
TABLES - INDIVIDUAL DATA	67
Mortality Data	68- 75
Clinical Signs, Daily	76- 84
Body Weight	85- 92
Body Weight Gain	93-100
Food Consumption	101-108
Relative Food Consumption	109-116
Ophthalmoscopic Examination	117-120
Haematology	121-132
Clinical Biochemistry	133-144
Macroscopic Findings	145-152
Organ Weights / Organ-Body Weight Ratios	153-160
APPENDIX	
(1) ANALYTICAL CHEMISTRY REPORT	1- 7
(2) PATHOLOGY REPORT	1- 62
TOTAL NUMBER OF PAGES	229

PREFACE

TEST SUBSTANCE

Identification TKK 30059 (ZK RT 1507)
Description White powder
Batch E-41650932
Purity >99%
Test substance storage At room temperature protected from light#

All test substance handlings were performed under red light conditions

Stability under storage conditions Stable
Expiry date December 31, 1994
Vehicle Corn oil, specific gravity 0.92
Stability in vehicle Stable in corn oil for at least 4 hours

The sponsor is responsible for the completeness and GLP Compliance of all test substance data.

TEST SUBSTANCE FORMULATION

Method Formulations (w/w) were prepared daily immediately prior to dosing. Adjustment was made for specific gravity of vehicle.
Storage conditions At ambient temperature protected from light.

CHEMICAL ANALYSIS OF DOSE PREPARATIONS

Analysis of formulations

Samples of pretreatment and week 1 formulations were analysed to check stability, homogeneity (highest and lowest concentration) and accuracy of preparations (all concentrations).

PURPOSE AND RATIONALE

The nature and purpose of this sub-acute toxicity study was to assess the toxic potential of TKK 30059 (ZK RT 1507) when administered to rats by daily oral gavage for a period of 28 days, followed by a 28-day recovery period.

This study should provide part of a rational basis for toxicological risk assessment in man. The oral route was selected as it is a possible route of human exposure during manufacture, handling or use of the test substance.

GUIDELINES

The study procedures described in this report were based on the following guidelines:

- 1) EEC Directive 92/69/EEC, Annex V of the EEC Directive 67/548/EEC, Part B : Methods for the Determination of Toxicity; B.7: "Sub-acute Toxicity - Oral". Official Journal of the European Communities No. L383, December 1992.
- 2) OECD "Guidelines for Testing of Chemicals", Section 4, Health Effects, No. 407, "Repeated Dose Oral Toxicity - Rodent: 28 or 14 day study", Paris Cedex, May 12, 1981.
- 3) Substance Law 1987 according to the notification of Dec. 9 1986 by EA, Environmental Agency (no. 700), MHW, Ministry of Health and Welfare (No. 1039) and MITI, Ministry of International Trade and Industry (No. 1014)

ARCHIVING

NOTOX B.V., will archive the following data for at least 10 years: protocol, raw data, report, test substance reference sample and all specimens. All magnetic media produced within NOTOX will be maintained indefinitely.

TEST SYSTEM

Test System	Albino rat, Wistar strain (outbred, SPF-Quality) Recognised by international guidelines as the recommended test system (e.g. EPA, FDA, OECD, EEC). Females were nulliparous and non-pregnant. Source : BRL Ltd., Basel, Switzerland
Age at Start of Treatment	Approximately 6 weeks.
Number of animals	30 males, 30 females
Randomisation	At least 5 days before study start, by computer-generated random algorithm according to body weight, with all animals within \pm 20% of the sex mean. A veterinary examination was performed prior to commencement of treatment to ensure that the animals were in a good state of health.
Identification	Earmark and tattoo

ALLOCATION

Group	Dose level mg/kg/day	Number of animals		Animal numbers	
		males	females	males	females
1 Main group	0	5	5	1- 5	31-35
1 Recovery group	0	5	5	6-10	36-40
2 Main group	5	5	5	11-15	41-45
3 Main group	50	5	5	16-20	46-50
4 Main group	250	5	5	21-25	51-55
4 Recovery group	250	5	5	26-30	56-60

ANIMAL HUSBANDRY**Conditions**

Air-conditioned room with approximately 15 air changes per hour and the environment controlled with optimal conditions considered as being a temperature of 21°C and a relative humidity of 50%. Fluctuations from these optimal conditions were noted, but were considered not to have affected study integrity. Lighting was 12 hours artificial fluorescent light and 12 hours dark per day. Dosing was performed under red light conditions.

Accommodation

Group housing of 5 animals per sex per cage in stainless steel suspended cages with wire mesh floors. The acclimatisation period was at least 5 days before start of treatment under laboratory conditions.

Diet

Free access to standard pelleted laboratory animal diet (Kliba 343 from Klingentalmühle AG, Kaiseraugst, Switzerland). Over the last four days of the recovery period, powdered diet (of the same composition) was presented in the cages of all recovery animals. Each batch was analysed for contaminants and results were examined and archived.

Water

Free access to tap-water. Certificates of analysis (performed quarterly) were examined and archived.

DOSE LEVEL SELECTION

A 5-day dose range finding study was performed (with 3 rats/sex/group at dose levels of 50, 200 and 1000 mg/kg/day) under NOTOX Project number 126293. Results were as follows:

Mortality	All animals of the 1000 mg/kg group died or were killed <u>in extremis</u> on days 3-4.
Clinical signs	Severe changes in clinical condition were noted in animals treated at 1000 mg/kg, and slight changes in one animal treated at 200 mg/kg.
Body weight	Body weight loss or low body weight gain in some animals of the 200 mg/kg group.
Food consumption	Not measured.
Macroscopic examination	Severely irritated stomach, haemorrhages in intestines and thymus, small spleen and enlarged adrenal glands in animals of the 1000 mg/kg group. Pale enlarged kidneys and small spleen in one animal treated at 200 mg/kg.
Liver/Kidney weight	High kidney weights in one male treated at 200 mg/kg.

Based on these observations, dose levels for a study of 28-days duration were selected to be 0, 5, 50 and 250 mg/kg/day.

TREATMENT

Method	Oral gavage, using a stainless steel stomach tube.
Frequency	Once daily for 28 days, approximately the same time each day, 7 days per week.
Dose Levels	Group 1: 0 mg/kg b.w./day (vehicle) Group 2: 5 mg/kg b.w./day Group 3: 50 mg/kg b.w./day Group 4: 250 mg/kg b.w./day
Dose volume	5 ml/kg body weight. Actual dose volumes were calculated weekly according to the latest body weight.

OBSERVATIONS

Mortality / Viability	Twice daily.
Clinical signs	At least once daily from day 1 onwards. The time of onset, degree and duration were recorded.
Body weights	Weekly and on the day preceding termination, prior to overnight fasting.

Food consumption	Weekly. (Powdered diet consumption during week 4 of recovery was determined 2 to 4 times.)
Water consumption	Subjective appraisal was maintained during the study, but no quantitative investigation introduced as no effect was suspected.
Ophthalmoscopic examinations	Both eyes were examined following instillation of tropicamide solution (5 mg/ml) during weeks 4 (all groups) and 8 (recovery groups).

CLINICAL LABORATORY INVESTIGATIONS

Blood samples were collected under light ether anaesthesia, between 7.30 and 9.30 a.m. The animals were fasted overnight before blood sampling, but water was provided. Blood samples were drawn from the retro-orbital sinus of all rats/sex/group and collected into tubes prepared with EDTA for haematological parameters (0.6 ml), with citrate for clotting tests (1.0 ml) and untreated tubes for clinical biochemistry parameters (>2.0 ml).

HAEMATOLOGY

The following haematology parameters were determined from blood containing EDTA as an anti-coagulant:

Parameter/Abbreviation	Unit	Instrumentation
Erythrocyte count/RBC	T/l	Sysmex K-1000
Haemoglobin/HB	mmol/l	Sysmex K-1000
Haematocrit/HCT	l/l	Sysmex K-1000
Mean corpuscular volume/MCV	f1	Sysmex K-1000
Mean corpuscular haemoglobin/MCH	fmol	Sysmex K-1000
Mean corpuscular haemoglobin concentration/MCHC	mmol/l	Sysmex K-1000
Platelet count	G/l	Sysmex K-1000
Red cell distribution width/RDW	%	Sysmex K-1000
Total leucocyte count/WBC	G/l	Sysmex K-1000
Differential leucocyte count/SEG (Neutrophils) EO (Eosinophils), BASO (Basophils), LYMPH (Lymphocytes), MONO (Monocytes)	1(rel)	Manual (Microscope)

The following haematology parameters were determined from blood containing citrate as an anti-coagulant:

Parameter/Abbreviation	Unit	Instrumentation/Method
Prothrombin time/PT	sec	Sysmex CA-5000
Partial thromboplastin time/PTT	sec	Sysmex CA-5000

CLINICAL BIOCHEMISTRY

The following clinical biochemistry parameters were determined from untreated blood samples after clotting and centrifugation:

Parameter/Abbreviation	Unit	Instrumentation
Alanine aminotransferase/ (ALAT/GPT)	ukat/l	Epos selective analyser 5060 (Eppendorf)
Aspartate aminotransferase/ (ASAT/GOT)	ukat/l	Epos selective analyser 5060 (Eppendorf)
Bilirubin, total/ BILI T.	umol/l	Epos selective analyser 5060 (Eppendorf)
Cholesterol, total/ CHOLEST. T.	mmol/l	Epos selective analyser 5060 (Eppendorf)
Triglycerides/ TRIGL.	mmol/l	Epos selective analyser 5060 (Eppendorf)
Creatinine	umol/l	Epos selective analyser 5060 (Eppendorf)
Glucose	mmol/l	Epos selective analyser 5060 (Eppendorf)
Urea	mmol/l	Epos selective analyser 5060 (Eppendorf)
Protein, total/ PROTEIN T.	g/l	Epos selective analyser 5060 (Eppendorf)
Protein, albumin/ ALBUMIN	g/l	Epos selective analyser 5060 (Eppendorf)
Protein, globulin/ GLOBULIN	g/l	Calculation [PROTEIN T.-ALBUMIN]
Albumin Globulin ratio A/G RATIO	1	Calculation [ALBUMIN/GL08]

Alkaline phosphatase/ ALP	ukat/l	Epos selective analyser 5060 (Eppendorf)
Sodium	mmol/l	Eppendorf Flame Photometer MFM 6350
Potassium	mmol/l	Eppendorf Flame Photometer MFM 6350
Chloride	mmol/l	Jenway PCLM3
Calcium	mmol/l	Eppendorf Flame Photometer MFM 6350
Phosphorus/ INORG. PHOSPH	mmol/l	Epos selective analyser 5060 (Eppendorf)

PATHOLOGY

NECROPSY

All animals surviving to the end of the observation period (day 29 for the Main Groups and day 57 for the Recovery Groups) were deeply anaesthetised using ether vapour and subsequently exsanguinated. All animals assigned to the study were necropsied and descriptions of all macroscopic abnormalities recorded.

Samples of the following tissues and organs were collected from all animals at necropsy and fixed in neutral phosphate buffered 4% formaldehyde solution:

- Adrenal glands
- Aorta
- Brain
- Caecum
- Cervix
- Clitoral gland
- Colon
- Duodenum
- Epididymides
- Eyes with optic nerve and Harderian gland
- Female mammary gland area
- Femur including joint
- Heart
- Ileum
- Jejunum
- Kidneys
- Larynx
- Lacrimal gland, exorbital
- Liver
- Lung, infused with formalin
- Lymph nodes - mandibular, mesenteric
- Nasopharynx
- Oesophagus
- Ovaries
- Pancreas

Pituitary gland
Preputial gland
Prostate gland
Rectum
Salivary glands - mandibular, sublingual
Sciatic nerve
Seminal vesicles
Skeletal muscle
Skin
Spinal cord -cervical, midthoracic, lumbar
Spleen
Sternum with bone marrow
Stomach
Testes
Thymus
Thyroid including parathyroid
Tongue
Trachea
Urinary bladder
Uterus
Vagina
All gross lesions

ORGAN WEIGHTS

The following organ weights (and terminal body weight) were recorded on the scheduled day of necropsy:

Adrenal glands
Brain
Heart
Kidneys
Liver
Ovaries
Spleen
Testes

HISTOTECHNOLOGY

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded and cut at a thickness of 2-4 micrometers and stained with haematoxylin and eosin.

HISTOPATHOLOGY

Slides of adrenals, heart, kidneys, liver, spleen, stomach and testes, collected at the scheduled sacrifice from all animals of the control and the high dose group, and all gross lesions of all animals were examined by a pathologist. Based on the treatment related morphologic changes, kidneys and stomach were also examined from all rats of groups 2 (5 mg/kg/day) and 3 (50 mg/kg/day). All abnormalities were described and included in the report.

STATISTICAL ANALYSIS

The following statistical methods were used to analyse the data:

Univariate one-way analysis of variance was used to assess the significance of intergroup differences.

If the variables could be assumed to follow a normal distribution, the Dunnett-test (many to one t-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex.

The Steel-test (many-one rank test) was applied when the data could not be assumed to follow a normal distribution.

The exact Fisher-test was applied to the ophthalmoscopic examination data.

All tests were two-sided and in all cases $p < 0.05$ was accepted as the lowest level of significance.

Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables.

Test statistics were calculated on the basis of exact values for means and pooled variances. Individual values, means and standard deviations may have been rounded off before printing. Therefore, two groups may display the same printed means for a given parameter, yet display different test statistics values.

References:

- C.W. Dunnett
A Multiple Comparison Procedure for Comparing Several Treatments with a Control,
J. Amer. Stat. Assoc. 50, 1096-1121 (1955).
- R.G. Miller
Simultaneous Statistical Inference, Springer Verlag, New York (1981).
- R.A. Fisher
Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

RESULTS

ANALYSIS OF DOSE PREPARATIONS (see Appendix 1)

Test substance formulations in corn oil were noted as stable for at least 4 hours and formed a homogeneous suspension at the concentrations tested. Analysis of the accuracy of dose preparations revealed values within the range of 91% to 109% of nominal, which was considered to represent an acceptable level of accuracy for formulations of this type.

OBSERVATIONS

MORTALITY

No mortality occurred during the study period.

CLINICAL SIGNS

There were no clinical signs of toxicity or behavioural changes over the 28 day treatment period.

During the last week of the recovery period, hunched posture and piloerection were noted in 2 males previously treated at 250 mg/kg. At the same time it was noted that the growth of the incisors was abnormal in males and females of the 250 mg/kg dose group. Incisors were white in colour, crooked, partly broken off and/or irregularly ground.

Other findings noted among treated and/or control animals during the course of the study were salivation, alopecia, scabs, brown discolouration of the skin around the nose and chromodacryorrhoea. These findings were considered not to be related to treatment. Salivation, particularly seen in animals receiving 250 mg/kg/day, is considered to be associated with oral treatment using a stomach tube and a possible bad taste or irritant effect of the test substance may have contributed to this.

BODY WEIGHT

Body weights and body weight gain of males of the 250 mg/kg dose group were decreased throughout the treatment period.

When body weight gain rate during the recovery period was considered, it was concluded that this was almost identical for control and 250 mg/kg treated males. In the graph, the slope of the weight gain curves are approximately equal for these two groups during the 4-week recovery phase.

In week 3 of the recovery period, slight body weight loss was seen for the males of the 250 mg/kg dose group. This effect coincided with and is considered to be the result of the observation of dental problems in these animals and associated food consumption values. When powdered diet was provided in the cages (in week 4 of recovery), it appeared that the animals regained their normal feeding pattern and showed body weight gain as could be expected from the first 2 weeks of recovery.

In females receiving 250 mg/kg, body weights and body weight gain were comparable to controls with the exception of week 4 of treatment, when a statistically significant decrease in body weight gain was seen.

Body weights and body weight gain of animals treated at 5 or 50 mg/kg/day remained in the same range as controls over the treatment and recovery period.

FOOD CONSUMPTION

During the treatment period, food consumption of males receiving 250 mg/kg was only marginally lower than values of control animals.

During week 3 of the recovery period, it was noted that food consumption was lower in males previously treated with 250 mg/kg/day. Again, this effect was attributed to the reduced ability to chew the pelleted diet because of the affected teeth. This is supported by the observation that after supplementation of the diet with powdered food (of identical composition), the body weight gain rate returned to normal.

Food consumption values for week 4 of the recovery are calculated from the overall consumption from pelleted and powder diet. As supplementation of powder diet in the animal cage is prone to spillage by the animals, the values appear to be unreasonably high for all groups. It might be carefully concluded that food consumption clearly improved in the 250 mg/kg treated males, but was still slightly lower than control values.

There were no differences in food consumption before or after allowance for body weight between animals treated at 5 or 50 mg/kg/day or females treated at 250 mg/kg/day and corresponding control animals.

OPHTHALMOSCOPIC EXAMINATION

There were no ophthalmology findings at weeks 4 and 8 that were attributed to treatment with the test substance.

Incidences and severity of findings were considered to be identical among treated and control animals.

CLINICAL LABORATORY INVESTIGATIONS

HAEMATOLOGY

Changes were noted in animals dosed at 250 mg/kg at the end of the 28-day treatment period. These included decreased values for red blood cell counts, haemoglobin, haematocrit and mean corpuscular volume (males only), increased values for red cell distribution width (males only) and differential neutrophilic leucocyte counts (both sexes). As a result, differential counts for lymphocytes were decreased.

After a 4-week recovery period, all red blood cell parameters had returned to normal but differential neutrophil counts were still increased, whereas relative lymphocyte counts were decreased.

Other statistically significant differences arising between controls and treated animals were considered to have arisen by chance and not to represent a change of biological significance.

Animals treated at 5 or 50 mg/kg for 28 days were considered not to be affected.

CLINICAL BIOCHEMISTRY

A broad range of biochemical changes in the blood were noted after 4 weeks of treatment at a dose level of 250 mg/kg.

The majority of changes were seen in only a limited number of animals of this dose group, indicating that the variation in physiological response is quite large. Effects were more pronounced in males than in females, and changes did not always reach statistical significance.

Findings are considered to be related with adverse effects on the liver (reflected in increased alanine aminotransferase and aspartate aminotransferase levels), kidney (reflected in elevations in creatinine and urea) and possibly with a deficient nutritional status (increased triglycerides and decreased levels of glucose, total protein, albumin, globulin).

Although changes in serum electrolytes showed little coherence, increased inorganic phosphate and decreased chloride levels may also be associated with nephrotoxic findings.

After a 4-week recovery period, evaluation of blood biochemistry revealed that all parameters had returned to normal, with the exception of increased creatinine and urea levels in one of the female animals of the 250 mg/kg dose group. This animal appeared to have developed a chronic interstitial nephritis. Increased protein levels noted in males of this treatment group were considered to represent a reactive effect on preceding disturbances.

There were no differences noted between control and rats receiving 5 or 50 mg/kg that were considered to be related to treatment with the test substance.

PATHOLOGY

MACROSCOPIC EXAMINATION

Macroscopic observations at necropsy revealed that kidneys were affected in males treated at 250 or 50 mg/kg for 4 weeks and the stomach in both males and females of these two dose groups. Findings noted were enlargement and pale appearance of the kidneys and thickening of the wall of the glandular stomach and/or limiting ridge.

After 4 weeks of recovery, the macroscopic appearance of these organs had returned to normal, with the exception of one female previously treated at 250 mg/kg, which showed an irregular surface of the kidneys and thickening of the limiting ridge of the stomach.

Among both males and females, the abnormal appearance of the incisors was confirmed here.

Other alterations noted among treated and control animals were considered to be within the range of biological variation for rats of this age and strain and not to represent a change of toxicological significance.

ORGAN WEIGHTS

To correct for decreased body weights of animals of the 250 mg/kg dose group after 4 weeks of treatment, organ:body weight ratios were considered for liver and kidneys. The relative weight of both of these organs was noted to be increased in males and females of the high dose group. A small but not statistically significant increase in relative kidney weights was seen in males of the 50 mg/kg dose group as well.

At the end of the 4-week recovery phase, kidney:body weight ratios were still increased in animals previously treated at 250 mg/kg, although the effect in females was only slight.

Other organ weights and relative organ weights of treated animals were considered to be similar to those of control animals. A statistically significant difference in adrenal weights in treated males, was considered to have resulted from a slightly low control value. Therefore, no toxicological significance was attached to this.

MICROSCOPIC EXAMINATION (see Appendix 2)

Histopathological evidence of toxicity was noted in the kidneys and the stomach.

After 4 weeks of treatment, kidneys of all treated males and of 250 mg/kg treated females were affected. Changes consisted of tubular dilation and degeneration, proteinaceous casts, increased amount of hyaline resorption bodies and urothelial hyperplasia.

After the 4 week recovery period, regenerative processes (basophilic tubules, fibrosis) were seen in the high dose males. In the high dose females, one female showed nephritis and the number of females with mineral deposition in the cortico-medullary region of the kidney was reduced.

In the stomach of nearly all animals of the 50 and 250 mg/kg dose groups changes were noted at the end of the treatment period. Findings recorded were gastritis and erosion of the glandular stomach and hyperkeratosis of the forestomach, which are indicative of a strong irritant effect of the test substance on the gastric wall.

After 4 weeks of recovery, gastritis was still seen for a few animals previously treated with 250 mg/kg.

The incisors were not examined histopathologically.

Other findings were considered not to be related to treatment as they were within the normal range of background alterations for rats of this age and strain.

DISCUSSION AND CONCLUSION

Test substance preparations in corn oil appeared to be stable and homogeneous and sufficiently accurate concentrations were encountered for the purpose of this study.

The primary target organ established in this subacute toxicity study with TKK 30059 (ZK RT 1507) was the kidney.

All treated males and females treated at 250 mg/kg showed extensive damage to the renal tubules which was reflected in changes in urea and creatinine levels in the blood, kidney weights and findings at autopsy and histopathology.

The principle role of the renal tubules is that of reabsorption of water, electrolytes and low molecular weight nutrients from the filtrate. From the tubular degeneration seen in this study, it might be anticipated that urine formation and subsequently blood homeostasis of these components would be severely affected. However, apart from increased phosphate and decreased chloride levels in the blood, no changes in electrolyte balance were demonstrated.

After 4 weeks of recovery, the kidney of nearly all high dose animals showed signs of regeneration and restoration of normal structure and function.

During the recovery period, males and females of the 250 mg/kg dose group were noted with incisors that were crooked, broken and showed irregular grinding. As a consequence, the opposite incisor in the other jaw was not subjected to proper wear and this resulted in overgrowth of that tooth.

The underlying mechanism is not clear and might be secondary to the renal toxicity caused during the treatment period. Tubular damage may have resulted in mineral loss and in order to maintain constant blood levels, minerals may have been released from other stores in the body i.e. bone and teeth. As a result, the teeth may have become more fragile.

Some evidence for this hypothesis might be derived from the microscopic observation that the number of females with mineralisation of the kidney was decreased in the female 250 mg/kg recovery group. The background incidence of this deposit of mainly calcium (in combination with phosphate) in the kidney of untreated females of this age and strain is nearly 100%.

Additional changes were related to anaemia, liver function, a possible deficit in the nutritional status of the animals and an irritant effect of the compound to the stomach.

Microcytic anaemia, seen after 4 weeks of treatment at 250 mg/kg, may have resulted from a diminished formation or red blood cells. No microscopic evidence was found for an increase in breakdown of erythrocytes.

An increase in metabolic activity of the hepatocytes after continuous exposure to a xenobiotic may have resulted in increased liver weights and increased serum enzymes, as noted in animals treated at 250 mg/kg for 28 days. No changes in liver structure indicative of liver toxicity were seen microscopically.

The nutritional status of the high dose animals might have been impaired, as was shown in altered triglyceride, glucose and protein levels in the blood. These changes are considered to be associated with the effects on body weight gain and food consumption.

In the stomach of animals treated at 50 or 250 mg/kg a number of changes were seen in response to an irritant effect of the test substance at these dose levels.

The increase in neutrophilic leucocytes, seen in 250 mg/kg treated animals both at week 4 and week 8, was considered to be a secondary effect, as these inflammatory cells probably proliferated to aid in clearing damaged areas in the kidney and stomach.

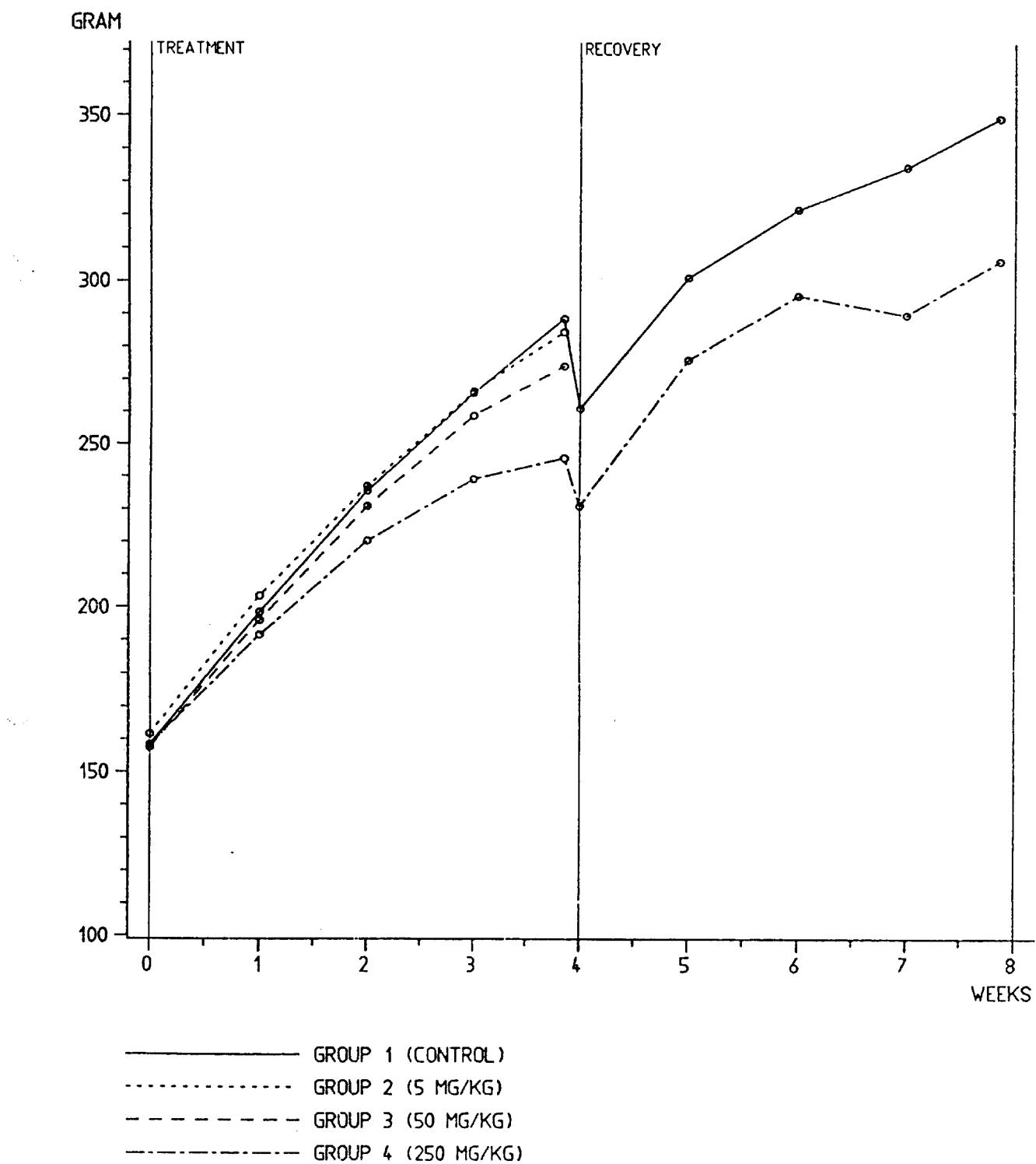
The results presented in this report demonstrated that rats of all dose groups showed signs of toxicity. Therefore, a definitive No Observed Effect Level (NOEL) could not be established.

TKK 30059 (ZK RT 1507)

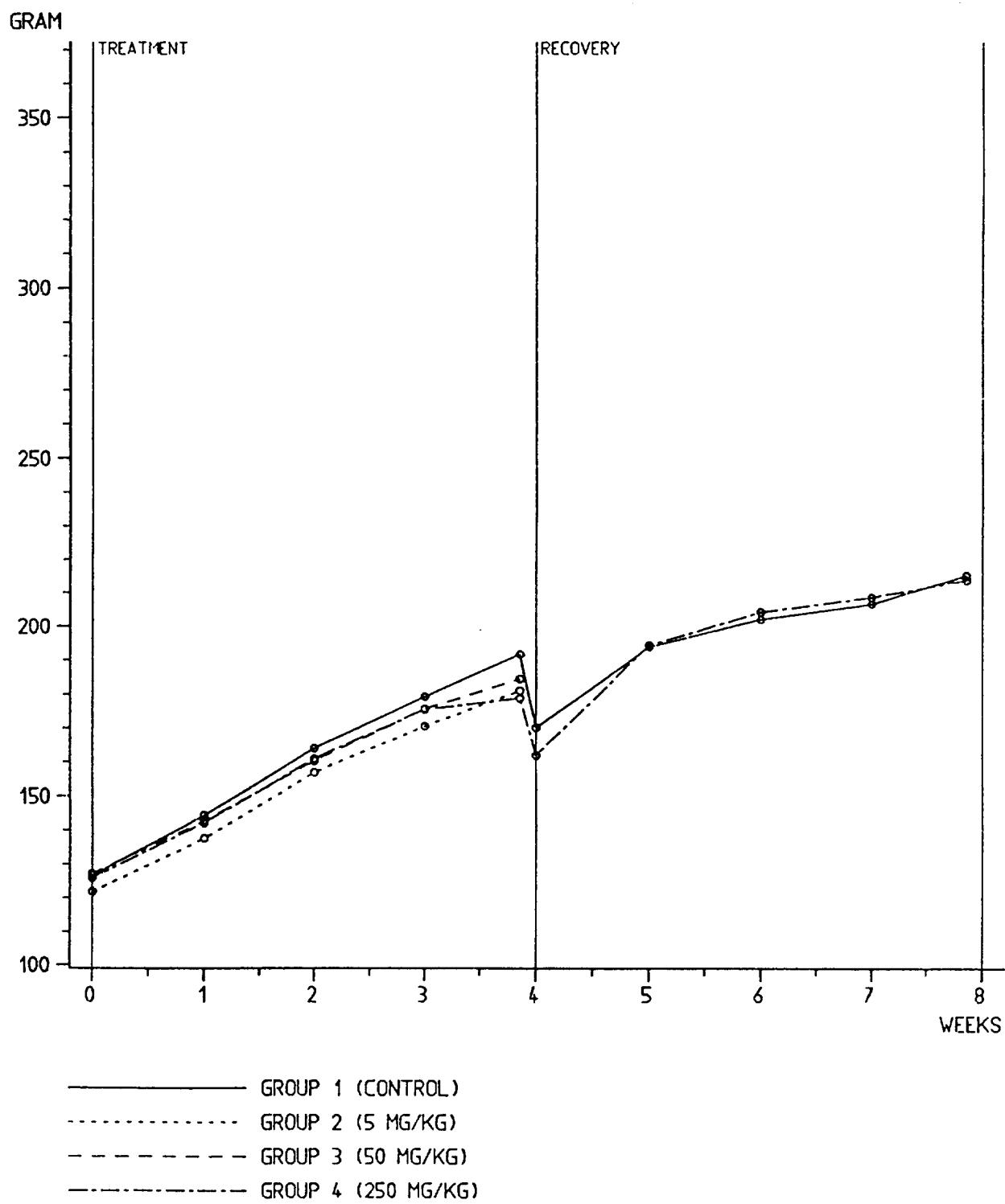
NOTOX Project 126282

FIGURES

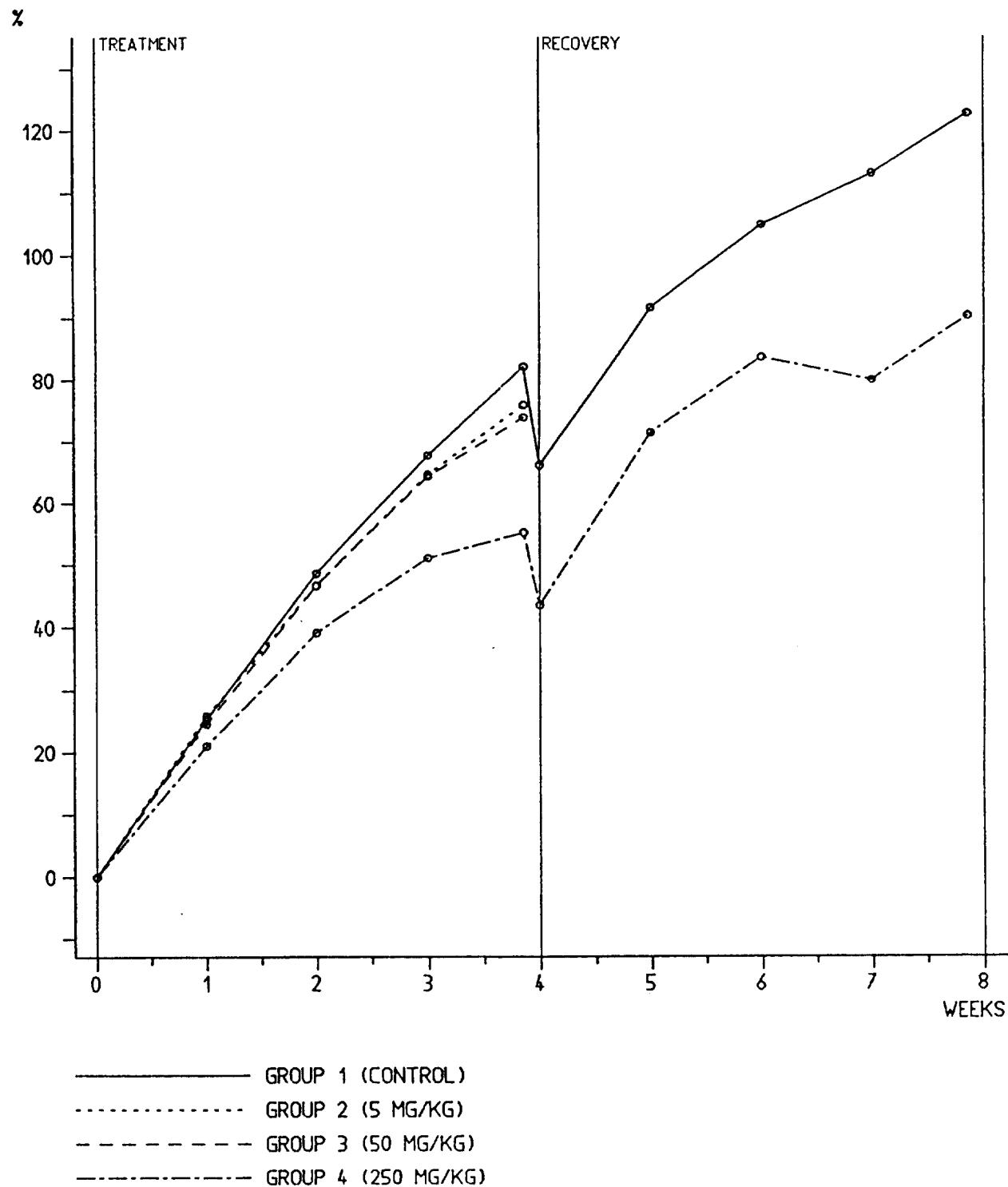
BODY WEIGHTS
MALES



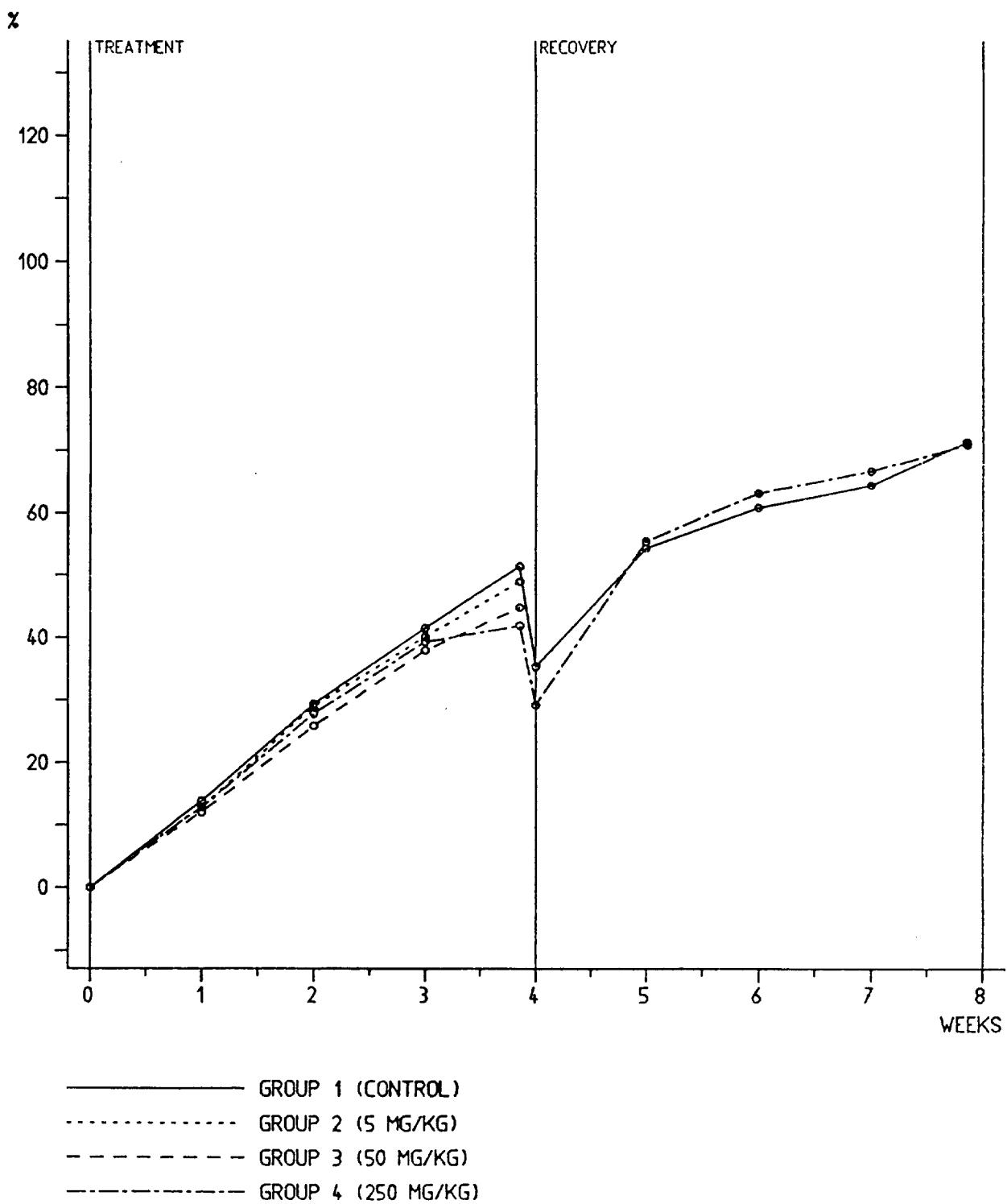
BODY WEIGHTS
FEMALES



BODY WEIGHT GAIN
MALES



BODY WEIGHT GAIN
FEMALES



TABLES - SUMMARY DATA

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

SYM-SUM - 1
06-OCT-94

CLINICAL SIGNS, DAILY (SUMMARY)
MALES
GROUP 1 (CONTROL)

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
SECRESSION / EXCRETION		
SALIVATION (3)	G:111..1.1.1.1.11.. %:111..1.1.1.1.11..

G: Median value of the highest individual daily grades
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%,..., A = more than 95%)

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

SYM-SUM - 2
06-OCT-94

**CLINICAL SIGNS, DAILY (SUMMARY)
MALES
GROUP 2 (5 MG/KG)**

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
------------------------------	----------------------------------------------	--------------------------------------

NO CLINICAL SIGNS NOTED

CLINICAL SIGNS, DAILY (SUMMARY)
MALES
GROUP 3 (50 MG/KG)

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
SECRESSION / EXCRETION		
SALIVATION (3)	G:1.1.1..... %:2.2.2.....	

G: Median value of the highest individual daily grades
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%,..., A = more than 95%)

CLINICAL SIGNS, DAILY (SUMMARY)
MALES
GROUP 4 (250 MG/KG)

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
POSTURE		
HUNCHED POSTURE (1)	G: %:11111112244444
SKIN / FUR / PLUMAGE		
PILOERECTION (1)	G: %:11111112244444
ALOPECIA (3) (NECK)	G:1111111 %:1111111
SKIN BROWN (1) (SNOUT)	G: %:	1..... 4.....
SECRESSION / EXCRETION		
SALIVATION (3)	G:1111111111111111 %:113222213122331122
CHROMODACRYORRHEA (3) (EYE LEFT)	G: %:111...222...
VARIOUS		
BROKEN (1) (UPPER INCISORS)	G: %:11111112222222

Note: incisors of all animals were white in colour, crooked, partly broken off and/or irregular grinding of incisors was seen from day 44 onwards.

G: Median value of the highest individual daily grades
 %: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%,..., A = more than 95%)

CLINICAL SIGNS, DAILY (SUMMARY)
FEMALES
GROUP 1 (CONTROL)

G: Median value of the highest individual daily grades
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%, ..., A = more than 95%)

CLINICAL SIGNS, DAILY (SUMMARY)
FEMALES
GROUP 2 (5 MG/KG)

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
SECRETION / EXCRETION		
SALIVATION (3)	G:1.... %:2....	

G: Median value of the highest individual daily grades
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%,.... A = more than 95%)

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

SYM-SUM - 7
06-OCT-94

**CLINICAL SIGNS, DAILY (SUMMARY)
FEMALES
GROUP 3 (50 MG/KG)**

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
NO CLINICAL SIGNS NOTED		

**CLINICAL SIGNS, DAILY (SUMMARY)
FEMALES
GROUP 4 (250 MG/KG)**

SIGN (MAX.GRADE) LOCATION	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
SKIN / FUR / PLUMAGE		
ALOPECIA (3) (HEAD)	G: %:	2221111111111111..... 222444444444422.....
SECRETION / EXCRETION		
SALIVATION (3)	G:1..1111111111111111 %:1..1241223312241933565

Note: incisors of all animals were white in colour, crooked, partly broken off and/or irregular grinding of incisors was seen from day 44 onwards.

G: Median value of the highest individual daily grades
%: Percent of affected animals (0 = less than 5%, 1 = between 5% and 15%,..., A = more than 95%)

**BODY WEIGHTS (GRAM) SUMMARY
 MALES**

TREATMENT			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1	MEAN		158	162	157	158
WEEK 1	ST.DEV.		8.3	6.8	13.6	6.1
	N		10	5	5	10
DAY 8	MEAN		199	203	196	192
WEEK 2	ST.DEV.		11.9	10.0	17.6	12.3
	N		10	5	5	10
DAY 15	MEAN		235	237	231	220
WEEK 3	ST.DEV.		12.3	12.6	19.6	14.3
	N		10	5	5	10
DAY 22	MEAN		266	266	259	239 **
WEEK 4	ST.DEV.		15.1	14.9	25.7	15.3
	N		10	5	5	10
DAY 28	MEAN		288	284	274	246 **
WEEK 4	ST.DEV.		14.3	17.4	28.9	18.5
	N		10	5	5	10

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHTS (GRAM) SUMMARY
MALES

RECOVERY			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1 WEEK 1	MEAN ST.DEV. N		261 16.7 5	---	---	231 19.3 5
DAY 8 WEEK 2	MEAN ST.DEV. N		301 15.6 5	---	---	276 16.0 5
DAY 15 WEEK 3	MEAN ST.DEV. N		321 14.5 5	---	---	295 17.5 5
DAY 22 WEEK 4	MEAN ST.DEV. N		334 16.6 5	---	---	289 26.4 5
DAY 28 WEEK 4	MEAN ST.DEV. N		349 17.5 5	---	---	306 14.1 5

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

**BODY WEIGHTS (GRAM) SUMMARY
FEMALES**

TREATMENT			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1	MEAN		127	122	127	126
WEEK 1	ST.DEV.		6.7	7.1	6.4	7.0
	N		10	5	5	10
DAY 8	MEAN		144	137	143	142
WEEK 2	ST.DEV.		10.5	7.6	9.8	7.5
	N		10	5	5	10
DAY 15	MEAN		164	157	160	161
WEEK 3	ST.DEV.		12.7	8.8	11.6	11.2
	N		10	5	5	10
DAY 22	MEAN		179	170	176	175
WEEK 4	ST.DEV.		14.1	8.0	14.2	11.3
	N		10	5	5	10
DAY 28	MEAN		192	181	184	179
WEEK 4	ST.DEV.		13.2	7.9	16.4	12.8
	N		10	5	5	10

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

**BODY WEIGHTS (GRAM) SUMMARY
 FEMALES**

RECOVERY			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1 WEEK 1	MEAN ST.DEV. N	170 7.6 5	---	0	0	162 15.8 5
DAY 8 WEEK 2	MEAN ST.DEV. N	194 9.6 5	---	0	0	194 16.2 5
DAY 15 WEEK 3	MEAN ST.DEV. N	202 9.1 5	---	0	0	204 16.9 5
DAY 22 WEEK 4	MEAN ST.DEV. N	207 11.2 5	---	0	0	209 18.5 5
DAY 28 WEEK 4	MEAN ST.DEV. N	215 7.1 5	---	0	0	214 15.6 5

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

**BODY WEIGHT GAIN (%) SUMMARY
MALES**

TREATMENT			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1	MEAN	0	0	0	0	0
WEEK 1	ST. DEV.	0.0	0.0	0.0	0.0	0.0
	N	10	5	5	5	10
DAY 8	MEAN	25	26	24	21	*
WEEK 2	ST. DEV.	2.4	2.5	0.9	4.4	
	N	10	5	5	10	
DAY 15	MEAN	49	47	47	39	**
WEEK 3	ST. DEV.	3.0	4.1	3.6	5.2	
	N	10	5	5	10	
DAY 22	MEAN	68	65	64	51	**
WEEK 4	ST. DEV.	4.8	4.9	6.5	6.1	
	N	10	5	5	10	
DAY 28	MEAN	82	76	74	55	**
WEEK 4	ST. DEV.	6.3	7.4	7.2	8.4	
	N	10	5	5	10	

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

**BODY WEIGHT GAIN (%) SUMMARY
 MALES**

RECOVERY			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1	MEAN	66	---	---	---	43 **
WEEK 1	ST.DEV.	5.0	---	---	0	9.8
	N	5	0	0	0	5
DAY 8	MEAN	92	---	---	---	71 **
WEEK 2	ST.DEV.	4.5	---	---	0	6.6
	N	5	0	0	0	5
DAY 15	MEAN	105	---	---	---	84 **
WEEK 3	ST.DEV.	6.0	---	---	0	7.4
	N	5	0	0	0	5
DAY 22	MEAN	113	---	---	---	80 **
WEEK 4	ST.DEV.	6.3	---	---	0	12.8
	N	5	0	0	0	5
DAY 28	MEAN	123	---	---	---	90 **
WEEK 4	ST.DEV.	7.9	---	---	0	4.8
	N	5	0	0	0	5

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

**BODY WEIGHT GAIN (%) SUMMARY
FEMALES**

TREATMENT			GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1 WEEK 1	MEAN ST.DEV. N		0 0.0 10	0 0.0 5	0 0.0 5	0 0.0 10
DAY 8 WEEK 2	MEAN ST.DEV. N		14 3.1 10	13 3.5 5	12 2.7 5	13 3.0 10
DAY 15 WEEK 3	MEAN ST.DEV. N		29 5.5 10	29 7.9 5	26 3.3 5	28 3.8 10
DAY 22 WEEK 4	MEAN ST.DEV. N		41 6.9 10	40 7.1 5	38 4.7 5	39 3.9 10
DAY 28 WEEK 4	MEAN ST.DEV. N		51 6.5 10	49 8.2 5	45 6.3 5	42 ** 5.0 10

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

**BODY WEIGHT GAIN (%) SUMMARY
FEMALES**

RECOVERY		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
DAY 1	MEAN	35	---	---	29
WEEK 1	ST.DEV.	4.2	---	---	6.1
	N	5	0	0	5
DAY 8	MEAN	54	---	---	55
WEEK 2	ST.DEV.	6.4	---	---	8.4
	N	5	0	0	5
DAY 15	MEAN	61	---	---	63
WEEK 3	ST.DEV.	5.5	---	---	7.2
	N	5	0	0	5
DAY 22	MEAN	64	---	---	67
WEEK 4	ST.DEV.	5.9	---	---	9.3
	N	5	0	0	5
DAY 28	MEAN	71	---	---	71
WEEK 4	ST.DEV.	8.5	---	---	8.7
	N	5	0	0	5

* / ** : Dunnett-Test based on pooled variance significant at 5% (*) or 1% (**) level

OPHTHALMOSCOPIC EXAMINATIONS SUMMARY
MALES

	GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
NO FINDINGS AT WEEK 4	8/10	5/5	3/5	9/10
AT WEEK 8	5/5	0/0	0/0	4/5
CHROMODACRYORRHEA AT WEEK 8	0/5	0/0	0/0	1/5
CORNEAL OPACITY AT WEEK 4	0/10	0/5	1/5	0/10
LENS OPACITY ANTERIOR AT WEEK 4	2/10	0/5	1/5	1/10

#/# : Fisher's Exact Test significant at level 5% (#) or 1% (##)

OPHTHALMOSCOPIC EXAMINATIONS SUMMARY
FEMALES

	GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
NO FINDINGS AT WEEK 4	9/10	5/5	4/5	8/10
AT WEEK 8	5/5	0/0	0/0	5/5
CHROMODACRYORRHEA AT WEEK 4	0/10	0/5	0/5	1/10
LENS OPACITY ANTERIOR AT WEEK 4	1/10	0/5	1/5	1/10

#/** : Fisher's Exact Test significant at level 5% (#) or 1% (**)

HAEMATOLOGY SUMMARY
AFTER 4 WEEKS
MALES

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
HAEMATOLOGY PARAMETERS					
RBC T/1	MEAN ST. DEV. N	7.48 0.39 10	7.69 0.40 5	7.39 0.60 5	6.90 * 0.44 10
HB mmol/l	MEAN ST. DEV. N	9.3 0.4 10	9.6 0.3 5	9.3 0.3 5	8.4 ** 0.4 10
HCT 1/l	MEAN ST. DEV. N	0.419 0.019 10	0.431 0.014 5	0.417 0.023 5	0.373 ** 0.020 10
MCV fl	MEAN ST. DEV. N	56.1 1.4 10	56.1 1.6 5	56.5 1.9 5	54.1 * 1.8 10
MCH fmol	MEAN ST. DEV. N	1.2 0.0 10	1.2 0.0 5	1.3 0.1 5	1.2 0.0 10
MCHC mmol/l	MEAN ST. DEV. N	22.2 0.2 10	22.2 0.2 5	22.3 0.4 5	22.5 0.4 10
RDW %	MEAN ST. DEV. N	11.7 0.6 10	11.5 0.6 5	11.8 0.6 5	13.0 ** 0.9 10
WBC G/l	MEAN ST. DEV. N	6.2 1.6 10	5.5 1.0 5	5.7 1.1 5	5.9 1.0 10
SEG. 1	MEAN ST. DEV. N	0.073 0.031 10	0.076 0.027 5	0.116 0.039 5	0.242 + 0.169 10
EO. 1	MEAN ST. DEV. N	0.006 0.007 10	0.002 0.003 5	0.004 0.004 5	0.007 0.006 10
BASO. 1	MEAN ST. DEV. N	0.000 0.000 10	0.000 0.000 5	0.000 0.000 5	0.000 0.000 10
MONO. 1	MEAN ST. DEV. N	0.020 0.015 10	0.011 0.009 5	0.021 0.011 5	0.017 0.014 10
LYMPH. 1	MEAN ST. DEV. N	0.903 0.033 10	0.911 0.033 5	0.859 0.034 5	0.735 + 0.171 10
PLATELETS G/l	MEAN ST. DEV. N	898 77 10	839 33 5	919 65 5	988 * 79 10
PT SEC	MEAN ST. DEV. N	14.8 0.9 9	14.5 0.8 5	14.6 0.6 4	13.5 ** 0.5 10
PTT SEC	MEAN ST. DEV. N	16.4 1.5 8	17.4 0.9 5	16.4 0.7 4	18.4 4.4 10

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**HAEMATOLOGY SUMMARY
AFTER 4 WEEKS
FEMALES**

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
HAEMATOLOGY PARAMETERS					
RBC T/l	MEAN ST.DEV. N	7.06 0.32 10	6.99 0.22 5	7.04 0.38 5	6.59 ** 0.29 9
HB mmol/l	MEAN ST.DEV. N	8.8 0.4 10	8.8 0.2 5	8.8 0.3 5	8.2 ** 0.4 9
HCT 1/l	MEAN ST.DEV. N	0.395 0.017 10	0.392 0.006 5	0.393 0.018 5	0.363 ** 0.019 9
MCV fl	MEAN ST.DEV. N	56.1 1.3 10	56.1 2.1 5	55.8 1.5 5	55.1 1.1 9
MCH fmol	MEAN ST.DEV. N	1.2 0.0 10	1.3 0.1 5	1.2 0.0 5	1.2 0.0 9
MCHC mmol/l	MEAN ST.DEV. N	22.2 0.2 10	22.5 0.6 5	22.3 0.4 5	22.5 0.3 9
RDW %	MEAN ST.DEV. N	11.2 0.6 10	10.8 0.3 5	11.0 0.4 5	11.7 0.6 9
WBC G/l	MEAN ST.DEV. N	3.2 0.8 10	2.9 0.8 5	3.8 1.3 5	3.8 1.3 9
SEG. 1	MEAN ST.DEV. N	0.115 0.045 10	0.078 0.015 5	0.097 0.029 5	0.183 0.084 9
EO. 1	MEAN ST.DEV. N	0.009 0.007 10	0.014 0.011 5	0.011 0.009 5	0.009 0.006 9
BASO. 1	MEAN ST.DEV. N	0.000 0.000 10	0.000 0.000 5	0.000 0.000 5	0.000 0.000 9
MONO. 1	MEAN ST.DEV. N	0.012 0.005 10	0.014 0.013 5	0.016 0.008 5	0.014 0.010 9
LYMPH. 1	MEAN ST.DEV. N	0.865 0.052 10	0.894 0.025 5	0.876 0.026 5	0.793 0.088 9
PLATELETS G/l	MEAN ST.DEV. N	838 85 10	840 53 5	887 103 5	989 ** 127 9
PT SEC	MEAN ST.DEV. N	15.9 0.6 9	16.0 0.6 4	15.2 0.4 5	15.3 0.4 10
PTT SEC	MEAN ST.DEV. N	17.8 1.9 9	20.0 3.4 4	17.6 0.8 5	16.7 2.1 10

/: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**HAEMATOLOGY SUMMARY
AFTER 8 WEEKS
MALES**

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
HAEMATOLOGY PARAMETERS			
RBC T/l	MEAN ST.DEV. N	8.11 0.31 5	8.06 0.33 5
HB mmol/l	MEAN ST.DEV. N	10.3 0.3 5	10.4 0.1 5
HCT 1/l	MEAN ST.DEV. N	0.441 0.013 5	0.449 0.013 5
MCV fl	MEAN ST.DEV. N	54.4 1.3 5	55.6 0.9 5
MCH fmol	MEAN ST.DEV. N	1.3 0.0 5	1.3 0.0 5
MCHC mmol/l	MEAN ST.DEV. N	23.4 0.4 5	23.2 0.4 5
RDW %	MEAN ST.DEV. N	14.2 0.4 5	14.5 1.6 5
WBC G/l	MEAN ST.DEV. N	7.0 1.3 5	5.6 0.8 5
SEG. 1	MEAN ST.DEV. N	0.109 0.019 5	0.185 0.086 5
EO. 1	MEAN ST.DEV. N	0.006 0.008 5	0.007 0.008 5
BASO. 1	MEAN ST.DEV. N	0.000 0.000 5	0.000 0.000 5
MONO. 1	MEAN ST.DEV. N	0.020 0.015 5	0.016 0.010 5
LYMPH. 1	MEAN ST.DEV. N	0.865 0.026 5	0.792 0.094 5
PLATELETS G/l	MEAN ST.DEV. N	865 53 5	925 116 5
PT SEC	MEAN ST.DEV. N	13.6 0.9 5	13.7 0.7 5
PTT SEC	MEAN ST.DEV. N	16.8 0.8 5	17.3 1.4 5

/: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**HAEMATOLOGY SUMMARY
AFTER 8 WEEKS
FEMALES**

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
HAEMATOLOGY PARAMETERS			
RBC T/l	MEAN ST.DEV. N	7.14 0.15 5	7.25 0.19 5
Hb mmol/l	MEAN ST.DEV. N	9.7 0.4 5	9.6 0.1 5
Hct 1/l	MEAN ST.DEV. N	0.409 0.013 5	0.412 0.004 5
MCV fl	MEAN ST.DEV. N	57.3 1.7 5	56.8 1.6 5
Mch fmol	MEAN ST.DEV. N	1.4 0.1 5	1.3 0.0 5
Mchc mmol/l	MEAN ST.DEV. N	23.6 0.3 5	23.4 0.3 5
RDW %	MEAN ST.DEV. N	13.1 0.8 5	13.0 0.3 5
Wbc G/l	MEAN ST.DEV. N	4.9 0.7 4	4.5 0.6 5
SEG. 1	MEAN ST.DEV. N	0.107 0.053 5	0.174 0.024 5
EO. 1	MEAN ST.DEV. N	0.006 0.007 5	0.013 0.006 5
BASO. 1	MEAN ST.DEV. N	0.000 0.000 5	0.000 0.000 5
MONO. 1	MEAN ST.DEV. N	0.006 0.005 5	0.015 0.011 5
LYMPH. 1	MEAN ST.DEV. N	0.881 0.057 5	0.798 0.026 5
PLATELETS G/l	MEAN ST.DEV. N	779 54 5	846 65 5
PT SEC	MEAN ST.DEV. N	14.7 0.7 5	13.7 1.0 4
PTT SEC	MEAN ST.DEV. N	16.1 1.2 5	15.5 1.5 4

/: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

CLINICAL BIOCHEMISTRY SUMMARY
AFTER 4 WEEKS
MALES

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
ALAT(GPT) ukat/l	MEAN ST.DEV. N	0.70 0.07 10	0.70 0.07 5	0.65 0.13 5	0.95 * 0.34 10
ASAT(GOT) ukat/l	MEAN ST.DEV. N	1.80 0.20 10	1.70 0.11 5	1.69 0.12 5	2.06 1.35 10
BILI T. umol/l	MEAN ST.DEV. N	2 0 10	2 0 5	2 1 5	2 0 9
CHOLEST.T. mmol/l	MEAN ST.DEV. N	2.15 0.19 10	2.16 0.18 5	2.26 0.20 5	2.28 0.42 10
TRIGL. mmol/l	MEAN ST.DEV. N	0.73 0.29 10	0.75 0.37 5	0.78 0.19 5	1.64 * 1.13 10
CREATININE umol/l	MEAN ST.DEV. N	36.2 2.7 10	36.0 3.8 5	40.8 1.6 5	43.2 ** 5.1 10
GLUCOSE mmol/l	MEAN ST.DEV. N	7.04 1.54 10	5.88 0.66 5	5.81 0.63 5	5.56 * 1.24 10
UREA mmol/l	MEAN ST.DEV. N	5.6 0.7 10	6.1 0.8 5	5.4 0.1 5	8.6 ** 1.6 10
PROTEIN T. g/l	MEAN ST.DEV. N	63 2 10	62 2 5	62 1 5	55 ** 4 10
ALBUMIN g/l	MEAN ST.DEV. N	33 1 10	33 1 5	31 1 5	29 ** 2 10
GLOBULIN g/l	MEAN ST.DEV. N	30 2 10	29 2 5	30 2 5	25 + 3 10
A/G RATIO	MEAN ST.DEV. N	1 0 10	1 0 5	1 0 5	1 0 10
ALP ukat/l	MEAN ST.DEV. N	6.17 1.07 10	5.77 0.87 5	5.61 1.47 5	4.90 1.56 10
SODIUM mmol/l	MEAN ST.DEV. N	141.1 1.9 10	142.6 1.1 5	141.8 0.7 5	140.6 2.1 10
POTASSIUM mmol/l	MEAN ST.DEV. N	4.32 0.37 10	4.55 0.39 5	4.16 0.29 5	4.18 0.38 10
CHLORIDE mmol/l	MEAN ST.DEV. N	96 2 10	98 3 5	95 2 5	93 ** 2 10
CALCIUM mmol/l	MEAN ST.DEV. N	2.58 0.08 10	2.59 0.03 5	2.52 0.05 5	2.52 0.12 10

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

CLINICAL BIOCHEMISTRY SUMMARY
AFTER 4 WEEKS
MALES

	GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
INORG PHOSPH mmol/l	MEAN 0.16	2.52	2.38	2.49
	ST.DEV. N	0.16 10	0.20 5	0.16 5
				3.19 ** 0.34 10

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

CLINICAL BIOCHEMISTRY SUMMARY
AFTER 4 WEEKS
FEMALES

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
ALAT(GPT) ukat/l	MEAN ST.DEV. N	0.55 0.09 10	0.55 0.16 5	0.48 0.07 5	0.75 0.31 10
ASAT(GOT) ukat/l	MEAN ST.DEV. N	1.58 0.15 10	1.66 0.20 5	1.59 0.21 5	2.47 2.80 10
BILI T. umol/l	MEAN ST.DEV. N	3 1 10	2 1 5	3 1 5	2 1 10
CHOLEST.T. mmol/l	MEAN ST.DEV. N	1.63 0.42 10	1.53 0.40 5	1.61 0.28 5	1.97 0.30 10
TRIGL. mmol/l	MEAN ST.DEV. N	0.43 0.09 10	0.36 0.04 5	0.69 0.50 5	1.42 ** 0.92 10
CREATININE umol/l	MEAN ST.DEV. N	35.2 5.2 10	38.0 5.5 5	34.6 2.7 5	39.5 9.2 10
GLUCOSE mmol/l	MEAN ST.DEV. N	5.32 0.26 10	5.34 0.33 5	5.54 0.71 5	5.00 0.80 10
UREA mmol/l	MEAN ST.DEV. N	7.2 1.8 10	6.9 1.4 5	6.7 1.1 5	8.1 3.0 10
PROTEIN T. g/l	MEAN ST.DEV. N	62 3 10	61 2 5	64 2 5	58 * 4 10
ALBUMIN g/l	MEAN ST.DEV. N	34 2 10	33 1 5	35 1 5	32 2 10
GLOBULIN g/l	MEAN ST.DEV. N	28 2 10	28 2 5	28 2 5	26 3 10
A/G RATIO	MEAN ST.DEV. N	1 0 10	1 0 5	1 0 5	1 0 10
ALP ukat/l	MEAN ST.DEV. N	3.22 0.77 10	3.02 0.66 5	2.71 0.53 5	3.14 0.66 10
SODIUM mmol/l	MEAN ST.DEV. N	140.3 1.1 10	141.9 1.2 5	141.4 1.2 5	141.7 1.6 10
POTASSIUM mmol/l	MEAN ST.DEV. N	4.14 0.37 10	4.11 0.22 5	4.00 0.18 5	3.85 0.20 10
CHLORIDE mmol/l	MEAN ST.DEV. N	99 1 10	101 2 5	99 3 5	97 3 10
CALCIUM mmol/l	MEAN ST.DEV. N	2.50 0.08 10	2.47 0.04 5	2.56 0.10 5	2.53 0.05 10

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

CLINICAL BIOCHEMISTRY SUMMARY
AFTER 4 WEEKS
FEMALES

	GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
INORG PHOSPH mmol/l	MEAN 0.31	1.79 0.22	2.09 0.20	2.29 0.41
N	10	5	5	10

/: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**CLINICAL BIOCHEMISTRY SUMMARY
AFTER 8 WEEKS
MALES**

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
ALAT(GPT) ukat/l	MEAN ST.DEV. N	0.58 0.04 5	0.51 0.12 5
ASAT(GOT) ukat/l	MEAN ST.DEV. N	1.63 0.07 5	1.83 0.23 5
BILI T. umol/l	MEAN ST.DEV. N	2 1 5	2 0 5
CHOLEST.T. mmol/l	MEAN ST.DEV. N	1.94 0.29 5	1.70 0.31 5
TRIGL. mmol/l	MEAN ST.DEV. N	1.34 0.73 5	0.94 0.33 5
CREATININE umol/l	MEAN ST.DEV. N	38.0 3.4 5	35.8 2.4 5
GLUCOSE mmol/l	MEAN ST.DEV. N	7.41 0.43 5	7.17 0.69 5
UREA mmol/l	MEAN ST.DEV. N	7.5 1.3 5	7.0 0.6 5
PROTEIN T. g/l	MEAN ST.DEV. N	64 1 5	68 * 3 5
ALBUMIN g/l	MEAN ST.DEV. N	31 1 5	32 2 5
GLOBULIN g/l	MEAN ST.DEV. N	33 1 5	37 3 5
A/G RATIO	MEAN ST.DEV. N	1 0 5	1 0 5
ALP ukat/l	MEAN ST.DEV. N	3.82 1.00 5	3.52 0.97 5
SODIUM mmol/l	MEAN ST.DEV. N	142.1 0.9 5	141.6 2.1 5
POTASSIUM mmol/l	MEAN ST.DEV. N	4.41 0.43 5	4.56 0.26 5
CHLORIDE mmol/l	MEAN ST.DEV. N	100 1 5	99 1 5
CALCIUM mmol/l	MEAN ST.DEV. N	2.52 0.03 5	2.46 0.06 5

/: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

CHE-SUM - 6
06-DEC-94

CLINICAL BIOCHEMISTRY SUMMARY
AFTER 8 WEEKS
MALES

	GROUP 1 CONTROL	GROUP 4 250 MG/KG	
INORG PHOSPH mmol/l	MEAN ST.DEV. N	2.15 0.12 5	2.16 0.18 5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

CLINICAL BIOCHEMISTRY SUMMARY
AFTER 8 WEEKS
FEMALES

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
ALAT(GPT) ukat/l	MEAN ST.DEV. N	0.49 0.08 5	0.45 0.07 5
ASAT(GOT) ukat/l	MEAN ST.DEV. N	1.40 0.17 5	1.45 0.23 5
BILI T. umol/l	MEAN ST.DEV. N	2 0 5	2 0 5
CHOLEST.T. mmol/l	MEAN ST.DEV. N	1.77 0.50 5	1.92 0.45 5
TRIGL. mmol/l	MEAN ST.DEV. N	0.45 0.15 5	0.73 0.40 5
CREATININE umol/l	MEAN ST.DEV. N	38.6 4.2 5	43.4 9.5 5
GLUCOSE mmol/l	MEAN ST.DEV. N	6.15 0.37 5	5.81 1.55 5
UREA mmol/l	MEAN ST.DEV. N	7.5 1.3 5	8.6 1.6 5
PROTEIN T. g/l	MEAN ST.DEV. N	66 3 5	69 2 5
ALBUMIN g/l	MEAN ST.DEV. N	33 1 5	33 1 5
GLOBULIN g/l	MEAN ST.DEV. N	33 3 5	35 1 5
A/G RATIO	MEAN ST.DEV. N	1 0 5	1 0 5
ALP ukat/l	MEAN ST.DEV. N	1.99 0.60 5	1.66 0.35 5
SODIUM mmol/l	MEAN ST.DEV. N	138.3 2.0 5	140.7 * 1.2 5
POTASSIUM mmol/l	MEAN ST.DEV. N	3.89 0.21 5	3.97 0.22 5
CHLORIDE mmol/l	MEAN ST.DEV. N	99 2 5	100 2 5
CALCIUM mmol/l	MEAN ST.DEV. N	2.46 0.09 5	2.45 0.06 5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

CHE-SUM - 8
06-DEC-94

**CLINICAL BIOCHEMISTRY SUMMARY
AFTER 8 WEEKS
FEMALES**

	GROUP 1 CONTROL	GROUP 4 250 MG/KG
INORG PHOSPH mmol/l	MEAN 0.30 ST.DEV. 5	1.81 0.19 1.66 5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 4 WEEKS
MALES**

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
BODY W.	MEAN	269	262	253	222 **
	ST. DEV.	13	15	26	18
	N	5	5	5	5
BRAIN	MEAN	1.88	1.90	1.85	1.89
	ST. DEV.	0.07	0.08	0.11	0.05
	N	5	5	5	5
HEART	MEAN	0.929	0.922	0.886	0.786 *
	ST. DEV.	0.073	0.099	0.046	0.059
	N	5	5	5	5
LIVER	MEAN	8.36	7.61	7.99	9.34
	ST. DEV.	0.88	0.88	0.97	1.57
	N	5	5	5	5
KIDNEYS	MEAN	1.70	1.82	2.08	3.07 **
	ST. DEV.	0.03	0.13	0.28	1.01
	N	5	5	5	5
ADRENALS	MEAN	0.051	0.060	0.066	0.071 *
	ST. DEV.	0.008	0.010	0.012	0.011
	N	5	5	5	5
SPLEEN	MEAN	0.582	0.565	0.515	0.498
	ST. DEV.	0.042	0.108	0.125	0.073
	N	5	5	5	5
TESTES	MEAN	3.26	3.34	3.20	3.10
	ST. DEV.	0.15	0.33	0.24	0.32
	N	5	5	5	5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BODY WEIGHT RATIOS SUMMARY
 AFTER 4 WEEKS
 MALES**

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
BODY W. (GRAM)	MEAN ST.DEV. N	269 13 5	262 15 5	253 26 5	222 ** 18 5
BRAIN (%)	MEAN ST.DEV. N	0.70 0.03 5	0.73 0.04 5	0.73 0.04 5	0.86 ** 0.08 5
HEART (%)	MEAN ST.DEV. N	0.345 0.026 5	0.352 0.034 5	0.351 0.027 5	0.355 0.033 5
LIVER (%)	MEAN ST.DEV. N	3.10 0.22 5	2.90 0.19 5	3.15 0.07 5	4.19 ** 0.45 5
KIDNEYS (%)	MEAN ST.DEV. N	0.63 0.03 5	0.70 0.04 5	0.82 0.09 5	1.37 ** 0.36 5
ADRENALS (%)	MEAN ST.DEV. N	0.019 0.004 5	0.023 0.003 5	0.026 * 0.004 5	0.032 ** 0.004 5
SPLEEN (%)	MEAN ST.DEV. N	0.216 0.019 5	0.215 0.037 5	0.201 0.031 5	0.224 0.022 5
TESTES (%)	MEAN ST.DEV. N	1.21 0.09 5	1.27 0.08 5	1.27 0.11 5	1.40 * 0.12 5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 4 WEEKS
FEMALES

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
BODY W.	MEAN	178	161	165	162
	ST.DEV.	13	7	15	10
	N	5	5	5	5
BRAIN	MEAN	1.79	1.73	1.75	1.78
	ST.DEV.	0.08	0.05	0.01	0.08
	N	5	5	5	5
HEART	MEAN	0.693	0.593 *	0.701	0.684
	ST.DEV.	0.062	0.040	0.060	0.048
	N	5	5	5	5
LIVER	MEAN	5.58	5.26	5.36	6.51 *
	ST.DEV.	0.44	0.46	0.42	0.82
	N	5	5	5	5
KIDNEYS	MEAN	1.36	1.25	1.29	1.48
	ST.DEV.	0.11	0.05	0.06	0.11
	N	5	5	5	5
ADRENALS	MEAN	0.071	0.069	0.070	0.075
	ST.DEV.	0.014	0.006	0.008	0.004
	N	5	5	5	5
SPLEEN	MEAN	0.496	0.461	0.433	0.386 *
	ST.DEV.	0.065	0.048	0.065	0.039
	N	5	5	5	5
OVARIES	MEAN	0.153	0.130	0.134	0.148
	ST.DEV.	0.015	0.026	0.013	0.022
	N	5	5	5	5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 4 WEEKS
FEMALES

		GROUP 1 CONTROL	GROUP 2 5 MG/KG	GROUP 3 50 MG/KG	GROUP 4 250 MG/KG
BODY W. (GRAM)	MEAN ST.DEV. N	178 13 5	161 7 5	165 15 5	162 10 5
BRAIN (%)	MEAN ST.DEV. N	1.01 0.06 5	1.08 0.06 5	1.06 0.11 5	1.09 0.03 5
HEART (%)	MEAN ST.DEV. N	0.389 0.018 5	0.370 0.027 5	0.426 0.042 5	0.421 0.018 5
LIVER (%)	MEAN ST.DEV. N	3.13 0.13 5	3.28 0.22 5	3.25 0.12 5	4.01 ** 0.39 5
KIDNEYS (%)	MEAN ST.DEV. N	0.77 0.03 5	0.78 0.04 5	0.79 0.08 5	0.91 ** 0.03 5
ADRENALS (%)	MEAN ST.DEV. N	0.040 0.007 5	0.043 0.002 5	0.042 0.006 5	0.046 0.005 5
SPLEEN (%)	MEAN ST.DEV. N	0.279 0.034 5	0.287 0.023 5	0.262 0.022 5	0.238 0.023 5
OVARIES (%)	MEAN ST.DEV. N	0.086 0.009 5	0.081 0.016 5	0.081 0.005 5	0.091 0.012 5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 8 WEEKS
MALES

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
BODY W.	MEAN	319	280 **
	ST.DEV.	16	17
	N	5	5
BRAIN	MEAN	1.96	1.87
	ST.DEV.	0.07	0.06
	N	5	5
HEART	MEAN	1.014	0.839
	ST.DEV.	0.129	0.133
	N	5	5
LIVER	MEAN	8.14	7.03 *
	ST.DEV.	0.88	0.51
	N	5	5
KIDNEYS	MEAN	1.78	1.96
	ST.DEV.	0.14	0.24
	N	5	5
ADRENALS	MEAN	0.069	0.062
	ST.DEV.	0.006	0.011
	N	5	5
SPLEEN	MEAN	0.510	0.533
	ST.DEV.	0.104	0.068
	N	5	5
TESTES	MEAN	3.26	3.43
	ST.DEV.	0.23	0.32
	N	5	5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

ORGAN/BODY WEIGHT RATIOS SUMMARY
AFTER 8 WEEKS
MALES

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
BODY W. (GRAM)	MEAN	319	280 **
	ST.DEV.	16	17
	N	5	5
BRAIN (%)	MEAN	0.61	0.67 *
	ST.DEV.	0.03	0.03
	N	5	5
HEART (%)	MEAN	0.317	0.299
	ST.DEV.	0.032	0.034
	N	5	5
LIVER (%)	MEAN	2.55	2.52
	ST.DEV.	0.18	0.14
	N	5	5
KIDNEYS (%)	MEAN	0.56	0.70 **
	ST.DEV.	0.02	0.08
	N	5	5
ADRENALS (%)	MEAN	0.022	0.022
	ST.DEV.	0.002	0.003
	N	5	5
SPLEEN (%)	MEAN	0.159	0.190
	ST.DEV.	0.031	0.018
	N	5	5
TESTES (%)	MEAN	1.02	1.23 *
	ST.DEV.	0.10	0.15
	N	5	5

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN WEIGHTS (GRAM) SUMMARY
AFTER 8 WEEKS
FEMALES**

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
BODY W.	MEAN ST.DEV. N	194 7 5	194 16 5
BRAIN	MEAN ST.DEV. N	1.76 0.07 5	1.81 0.08 5
HEART	MEAN ST.DEV. N	0.709 0.052 5	0.722 0.068 5
LIVER	MEAN ST.DEV. N	5.52 0.55 5	5.98 0.94 5
KIDNEYS	MEAN ST.DEV. N	1.35 0.14 5	1.52 0.27 5
ADRENALS	MEAN ST.DEV. N	0.073 0.005 5	0.081 0.021 5
SPLEEN	MEAN ST.DEV. N	0.398 0.043 5	0.497 0.118 5
OVARIES	MEAN ST.DEV. N	0.155 0.019 5	0.163 0.027 5

/: Dunnett-test based on pooled variance sig. at 5% or 1% level.

**ORGAN/BODY WEIGHT RATIOS SUMMARY
 AFTER 8 WEEKS
 FEMALES**

		GROUP 1 CONTROL	GROUP 4 250 MG/KG
BODY W. (GRAM)	MEAN ST.DEV. N	194 7 5	194 16 5
BRAIN (%)	MEAN ST.DEV. N	0.91 0.05 5	0.94 0.10 5
HEART (%)	MEAN ST.DEV. N	0.365 0.019 5	0.373 0.025 5
LIVER (%)	MEAN ST.DEV. N	2.85 0.31 5	3.07 0.24 5
KIDNEYS (%)	MEAN ST.DEV. N	0.70 0.08 5	0.78 0.11 5
ADRENALS (%)	MEAN ST.DEV. N	0.037 0.003 5	0.041 0.009 5
SPLEEN (%)	MEAN ST.DEV. N	0.205 0.017 5	0.255 0.049 5
OVARIES (%)	MEAN ST.DEV. N	0.080 0.007 5	0.084 0.010 5

/: Dunnett-test based on pooled variance sig. at 5% or 1% level.

TABLES - INDIVIDUAL DATA

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 1
07-OCT-94

**MORTALITY DATA
MALES
GROUP 1 (CONTROL)**

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
1	31-AUG-94	03-AUG-94	30-AUG-94
2	31-AUG-94	03-AUG-94	30-AUG-94
3	31-AUG-94	03-AUG-94	30-AUG-94
4	31-AUG-94	03-AUG-94	30-AUG-94
5	31-AUG-94	03-AUG-94	30-AUG-94
6	28-SEP-94	03-AUG-94	30-AUG-94
7	28-SEP-94	03-AUG-94	30-AUG-94
8	28-SEP-94	03-AUG-94	30-AUG-94
9	28-SEP-94	03-AUG-94	30-AUG-94
10	28-SEP-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 2
07-OCT-94

MORTALITY DATA
MALES
GROUP 2 (5 MG/KG)

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
11	31-AUG-94	03-AUG-94	30-AUG-94
12	31-AUG-94	03-AUG-94	30-AUG-94
13	31-AUG-94	03-AUG-94	30-AUG-94
14	31-AUG-94	03-AUG-94	30-AUG-94
15	31-AUG-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 3
07-OCT-94

MORTALITY DATA
MALES
GROUP 3 (50 MG/KG)

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	T0
16	31-AUG-94	03-AUG-94	30-AUG-94
17	31-AUG-94	03-AUG-94	30-AUG-94
18	31-AUG-94	03-AUG-94	30-AUG-94
19	31-AUG-94	03-AUG-94	30-AUG-94
20	31-AUG-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 4
07-OCT-94

MORTALITY DATA
MALES
GROUP 4 (250 MG/KG)

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
21	31-AUG-94	03-AUG-94	30-AUG-94
22	31-AUG-94	03-AUG-94	30-AUG-94
23	31-AUG-94	03-AUG-94	30-AUG-94
24	31-AUG-94	03-AUG-94	30-AUG-94
25	31-AUG-94	03-AUG-94	30-AUG-94
26	28-SEP-94	03-AUG-94	30-AUG-94
27	28-SEP-94	03-AUG-94	30-AUG-94
28	28-SEP-94	03-AUG-94	30-AUG-94
29	28-SEP-94	03-AUG-94	30-AUG-94
30	28-SEP-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 5
07-OCT-94

**MORTALITY DATA
FEMALES
GROUP 1 (CONTROL)**

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
31	31-AUG-94	03-AUG-94	30-AUG-94
32	31-AUG-94	03-AUG-94	30-AUG-94
33	31-AUG-94	03-AUG-94	30-AUG-94
34	31-AUG-94	03-AUG-94	30-AUG-94
35	31-AUG-94	03-AUG-94	30-AUG-94
36	28-SEP-94	03-AUG-94	30-AUG-94
37	28-SEP-94	03-AUG-94	30-AUG-94
38	28-SEP-94	03-AUG-94	30-AUG-94
39	28-SEP-94	03-AUG-94	30-AUG-94
40	28-SEP-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 6
07-OCT-94

**MORTALITY DATA
FEMALES
GROUP 2 (5 MG/KG)**

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
41	31-AUG-94	03-AUG-94	30-AUG-94
42	31-AUG-94	03-AUG-94	30-AUG-94
43	31-AUG-94	03-AUG-94	30-AUG-94
44	31-AUG-94	03-AUG-94	30-AUG-94
45	31-AUG-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 7
07-OCT-94

**MORTALITY DATA
FEMALES
GROUP 3 (50 MG/KG)**

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
46	31-AUG-94	03-AUG-94	30-AUG-94
47	31-AUG-94	03-AUG-94	30-AUG-94
48	31-AUG-94	03-AUG-94	30-AUG-94
49	31-AUG-94	03-AUG-94	30-AUG-94
50	31-AUG-94	03-AUG-94	30-AUG-94

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MORT-IND - 8
07-OCT-94

**MORTALITY DATA
FEMALES
GROUP 4 (250 MG/KG)**

ANIMAL	SCHEDULED NECROPSY	TREATMENT FROM	TO
51	31-AUG-94	03-AUG-94	30-AUG-94
52	31-AUG-94	03-AUG-94	30-AUG-94
53	31-AUG-94	03-AUG-94	30-AUG-94
54	31-AUG-94	03-AUG-94	30-AUG-94
55	31-AUG-94	03-AUG-94	30-AUG-94
56	28-SEP-94	03-AUG-94	30-AUG-94
57	28-SEP-94	03-AUG-94	30-AUG-94
58	28-SEP-94	03-AUG-94	30-AUG-94
59	28-SEP-94	03-AUG-94	30-AUG-94
60	28-SEP-94	03-AUG-94	30-AUG-94

CLINICAL SIGNS, DAILY
MALES
GROUP 1 (CONTROL)

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 1		
NO CLINICAL SIGNS NOTED		
ANIMAL 2		
NO CLINICAL SIGNS NOTED		
ANIMAL 3		
NO CLINICAL SIGNS NOTED		
ANIMAL 4		
NO CLINICAL SIGNS NOTED		
ANIMAL 5		
NO CLINICAL SIGNS NOTED		
ANIMAL 6		
NO CLINICAL SIGNS NOTED		
ANIMAL 7		
SECRETION / EXCRETION SALIVATION (3)	G:1...
ANIMAL 8		
NO CLINICAL SIGNS NOTED		
ANIMAL 9		
NO CLINICAL SIGNS NOTED		
ANIMAL 10		
SECRETION / EXCRETION SALIVATION (3)	G:111..1.1.1.1..1..

G: Highest daily grades

**CLINICAL SIGNS, DAILY
MALES
GROUP 2 (5 MG/KG)**

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 11		
NO CLINICAL SIGNS NOTED		
ANIMAL 12		
NO CLINICAL SIGNS NOTED		
ANIMAL 13		
NO CLINICAL SIGNS NOTED		
ANIMAL 14		
NO CLINICAL SIGNS NOTED		
ANIMAL 15		
NO CLINICAL SIGNS NOTED		

**CLINICAL SIGNS, DAILY
MALES
GROUP 3 (50 MG/KG)**

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 16		
SECRETION / EXCRETION SALIVATION (3)	G:1.1.....	
ANIMAL 17		
SECRETION / EXCRETION SALIVATION (3)	G:1.....	
ANIMAL 18		
NO CLINICAL SIGNS NOTED		
ANIMAL 19		
NO CLINICAL SIGNS NOTED		
ANIMAL 20		
NO CLINICAL SIGNS NOTED		

G: Highest daily grades

**CLINICAL SIGNS, DAILY
MALES
GROUP 4 (250 MG/KG)**

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 21		
SKIN / FUR / PLUMAGE ALOPECIA (3) (NECK)	G:111111.....	
SECRETION / EXCRETION SALIVATION (3)	G:1.....	
ANIMAL 22		
NO CLINICAL SIGNS NOTED		
ANIMAL 23		
NO CLINICAL SIGNS NOTED		
ANIMAL 24		
NO CLINICAL SIGNS NOTED		
ANIMAL 25		
SECRETION / EXCRETION SALIVATION (3)	G:1.....	
ANIMAL 26		
POSTURE HUNCHED POSTURE (1)	G:1111111.....	1111111
SKIN / FUR / PLUMAGE PILOERCTION (1)	G:1111111.....	1111111
SKIN BROWN (1) (SNOUT)	G:1.....	1.....
SECRETION / EXCRETION CHROMODACRYORRHEA (3) (EYE LEFT)	G:111...1111111.....	111...1111111
VARIOUS BROKEN (1) (UPPER INCISORS)	G:1111111.....	1111111
ANIMAL 27		
SECRETION / EXCRETION SALIVATION (3)	G:11111111..11..1.....	11111111..11..1.....
ANIMAL 28		
POSTURE HUNCHED POSTURE (1)	G:1111111.....	1111111
SKIN / FUR / PLUMAGE PILOERCTION (1)	G:1111111.....	1111111
SECRETION / EXCRETION SALIVATION (3)	G:11...1.1111111111.....	11...1.1111111111.....
ANIMAL 29		
SKIN / FUR / PLUMAGE SKIN BROWN (1) (SNOUT)	G:1.....	1.....
SECRETION / EXCRETION SALIVATION (3)	G:111.111111..1111111.....	111.111111..1111111.....
ANIMAL 30		
NO CLINICAL SIGNS NOTED		

Note: incisors of all animals were white in colour, crooked, partly broken off and/or irregular grinding of incisors was seen from day 44 onwards.

G: Highest daily grades

**CLINICAL SIGNS, DAILY
FEMALES
GROUP 1 (CONTROL)**

G: Highest daily grades

CLINICAL SIGNS, DAILY
FEMALES
GROUP 1 (CONTROL)

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 40		

SKIN / FUR / PLUMAGE		
ALOPECIA (3) (HEAD)	G:1.....
ALOPECIA (3) (NECK)	G:2222222.....
SCABS (3) (NECK)	G:11.....

G: Highest daily grades



**CLINICAL SIGNS, DAILY
FEMALES
GROUP 2 (5 MG/KG)**

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 41		
NO CLINICAL SIGNS NOTED		
ANIMAL 42		
NO CLINICAL SIGNS NOTED		
ANIMAL 43		
NO CLINICAL SIGNS NOTED		
ANIMAL 44		
NO CLINICAL SIGNS NOTED		
ANIMAL 45		
SECRETION / EXCRETION SALIVATION (3)	G:	1....

G: Highest daily grades

**CLINICAL SIGNS, DAILY
FEMALES
GROUP 3 (50 MG/KG)**

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 46		
NO CLINICAL SIGNS NOTED		
ANIMAL 47		
NO CLINICAL SIGNS NOTED		
ANIMAL 48		
NO CLINICAL SIGNS NOTED		
ANIMAL 49		
NO CLINICAL SIGNS NOTED		
ANIMAL 50		
NO CLINICAL SIGNS NOTED		

**CLINICAL SIGNS, DAILY
 FEMALES
 GROUP 4 (250 MG/KG)**

SIGN (MAX.GRADE) (LOCATION)	TREATMENT WEEKS: 1.....2.....3.....4.....	RECOVERY 1.....2.....3.....4.....
ANIMAL 51		
SECRETION / EXCRETION SALIVATION (3)	G:1.....1.1111	
ANIMAL 52		
NO CLINICAL SIGNS NOTED		
ANIMAL 53		
SECRETION / EXCRETION SALIVATION (3)	G:1.1111111111111111	
ANIMAL 54		
SECRETION / EXCRETION SALIVATION (3)	G:1....1....1..1..	
ANIMAL 55		
SECRETION / EXCRETION SALIVATION (3)	G:1....	
ANIMAL 56		
SECRETION / EXCRETION SALIVATION (3)	G:1....	
ANIMAL 57		
SKIN / FUR / PLUMAGE ALOPECIA (3) (HEAD)	G:	2221111111111111.....
SECRETION / EXCRETION SALIVATION (3)	G:1.1...11	
ANIMAL 58		
SECRETION / EXCRETION SALIVATION (3)	G:11..11	
ANIMAL 59		
SECRETION / EXCRETION SALIVATION (3)	G:11.11.1.111.1..11.	
ANIMAL 60		
SKIN / FUR / PLUMAGE ALOPECIA (3) (HEAD)	G:1111111111.....
SECRETION / EXCRETION SALIVATION (3)	G:1...11...1....1.11111.	

Note: incisors of all animals were white in colour, crooked, partly broken off and/or irregular grinding of incisors was seen from day 44 onwards.

G: Highest daily grades

**BODY WEIGHTS (GRAM)
MALES**

GROUP 1 (CONTROL)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3

1	162	203	239	268	291	---	---	---
2	159	194	230	257	282	---	---	---
3	170	213	251	288	310	---	---	---
4	146	185	224	257	285	---	---	---
5	162	202	244	275	302	---	---	---
6	152	194	229	252	271	248	296	312
7	156	195	237	270	294	268	304	324
8	166	215	246	282	298	283	321	344
9	146	177	210	237	262	241	278	306
10	165	207	244	269	287	264	304	321

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4

1	---	---
2	---	---
3	---	---
4	---	---
5	---	---
6	323	339
7	338	352
8	360	378
9	317	333
10	334	345

**BODY WEIGHTS (GRAM)
MALES**

GROUP 2 (5 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
11	163	210	249	280	305	---	---	---
12	151	186	216	241	258	---	---	---
13	162	204	237	270	291	---	---	---
14	162	207	240	266	279	---	---	---
15	170	210	243	273	288	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
11	---	---
12	---	---
13	---	---
14	---	---
15	---	---

**BODY WEIGHTS (GRAM)
MALES**

GROUP 3 (50 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
16	161	199	231	251	266	---	---	---
17	147	183	219	245	259	---	---	---
18	140	174	208	232	243	---	---	---
19	166	206	236	266	282	---	---	---
20	173	218	260	299	319	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
16	---	---
17	---	---
18	---	---
19	---	---
20	---	---

BODY WEIGHTS (GRAM)
MALES

GROUP 4 (250 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1	8	15	22	28	1	8	15
	1	2	3	4	4	1	2	3
21	165	205	234	246	258	---	---	---
22	152	177	208	227	230	---	---	---
23	154	186	213	237	243	---	---	---
24	150	179	207	219	217	---	---	---
25	157	198	226	244	257	---	---	---
26	152	183	206	233	244	224	263	283
27	163	199	227	247	259	236	279	302
28	167	215	251	274	281	262	302	323
29	159	184	216	226	234	218	269	284
30	163	189	214	238	233	214	265	284

DAYS WEEKS ANIMAL	RECOVERY	
	22	28
	4	4
21	---	---
22	---	---
23	---	---
24	---	---
25	---	---
26	270	292
27	289	308
28	333	329
29	288	300
30	267	300

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

BW-IND - 5
06-OCT-94

**BODY WEIGHTS (GRAM)
FEMALES**

GROUP 1 (CONTROL)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
31	132	154	176	197	210	---	---	---
32	132	160	182	195	210	---	---	---
33	131	149	179	199	206	---	---	---
34	124	138	157	169	179	---	---	---
35	118	134	158	175	184	---	---	---
36	120	134	147	164	183	164	191	197
37	121	135	153	165	180	163	194	200
38	120	133	151	165	180	170	185	196
39	131	149	162	176	184	171	189	199
40	137	156	174	187	200	182	210	218

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
31	---	---
32	---	---
33	---	---
34	---	---
35	---	---
36	195	217
37	207	214
38	202	208
39	204	210
40	225	226

**BODY WEIGHTS (GRAM)
FEMALES**

GROUP 2 (5 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
41	115	127	144	157	168	---	---	---
42	130	143	153	171	180	---	---	---
43	117	132	158	175	186	---	---	---
44	118	140	162	171	183	---	---	---
45	129	145	167	178	188	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
41	---	---
42	---	---
43	---	---
44	---	---
45	---	---

BODY WEIGHTS (GRAM)
FEMALES

GROUP 3 (50 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
46	132	149	166	187	197	---	---	---
47	121	134	152	166	174	---	---	---
48	120	130	145	156	161	---	---	---
49	134	151	174	189	199	---	---	---
50	129	149	164	180	191	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
46	---	---
47	---	---
48	---	---
49	---	---
50	---	---

BODY WEIGHTS (GRAM)
FEMALES

GROUP 4 (250 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
51	120	137	154	164	166	---	---	---
52	130	147	171	190	194	---	---	---
53	128	143	164	179	180	---	---	---
54	125	149	163	174	175	---	---	---
55	130	144	166	182	188	---	---	---
56	141	154	179	191	195	180	209	223
57	119	136	152	162	166	151	179	185
58	121	133	155	174	176	156	198	204
59	127	146	166	180	189	177	210	219
60	118	131	139	153	158	145	176	190

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
51	---	---
52	---	---
53	---	---
54	---	---
55	---	---
56	226	227
57	186	196
58	210	216
59	227	230
60	194	199

**BODY WEIGHT GAIN (%)
MALES**

GROUP 1 (CONTROL)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3

1	0	25	48	65	80	---	---	---
2	0	22	45	62	77	---	---	---
3	0	25	48	69	82	---	---	---
4	0	27	53	76	95	---	---	---
5	0	25	51	70	86	---	---	---
6	0	28	51	66	78	63	95	105
7	0	25	52	73	88	72	95	108
8	0	30	48	70	80	70	93	107
9	0	21	44	62	79	65	90	110
10	0	25	48	63	74	60	84	95

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4

1	---	---
2	---	---
3	---	---
4	---	---
5	---	---
6	113	123
7	117	126
8	117	128
9	117	128
10	102	109

**BODY WEIGHT GAIN (%)
MALES**

GROUP 2 (5 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
11	0	29	53	72	87	---	---	---
12	0	23	43	60	71	---	---	---
13	0	26	46	67	80	---	---	---
14	0	28	48	64	72	---	---	---
15	0	24	43	61	69	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
11	---	---
12	---	---
13	---	---
14	---	---
15	---	---

BODY WEIGHT GAIN (%)
MALES

GROUP 3 (50 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
16	0	24	43	56	65	---	---	---
17	0	24	49	67	76	---	---	---
18	0	24	49	66	74	---	---	---
19	0	24	42	60	70	---	---	---
20	0	26	50	73	84	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
16	---	---
17	---	---
18	---	---
19	---	---
20	---	---

**BODY WEIGHT GAIN (%)
 MALES**

GROUP 4 (250 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1	8	15	22	28	1	8	15
	1	2	3	4	4	1	2	3
21	0	24	42	49	56	---	---	---
22	0	16	37	49	51	---	---	---
23	0	21	38	54	58	---	---	---
24	0	19	38	46	45	---	---	---
25	0	26	44	55	64	---	---	---
26	0	20	36	53	61	47	73	86
27	0	22	39	52	59	45	71	85
28	0	29	50	64	68	57	81	93
29	0	16	36	42	47	37	69	79
30	0	16	31	46	43	31	63	74

DAYS WEEKS ANIMAL	RECOVERY	
	22	28
	4	4
21	---	---
22	---	---
23	---	---
24	---	---
25	---	---
26	78	92
27	77	89
28	99	97
29	81	89
30	64	84

**BODY WEIGHT GAIN (%)
FEMALES**

GROUP 1 (CONTROL)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3

31	0	17	33	49	59	---	---	---
32	0	21	38	48	59	---	---	---
33	0	14	37	52	57	---	---	---
34	0	11	27	36	44	---	---	---
35	0	14	34	48	56	---	---	---
36	0	12	23	37	53	37	59	64
37	0	12	26	36	49	35	60	65
38	0	11	26	38	50	42	54	63
39	0	14	24	34	40	31	44	52
40	0	14	27	36	46	33	53	59

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4

31	---	---
32	---	---
33	---	---
34	---	---
35	---	---
36	63	81
37	71	77
38	68	73
39	56	60
40	64	65

BODY WEIGHT GAIN (%)
FEMALES

GROUP 2 (5 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
41	0	10	25	37	46	---	---	---
42	0	10	18	32	38	---	---	---
43	0	13	35	50	59	---	---	---
44	0	19	37	45	55	---	---	---
45	0	12	29	38	46	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
41	---	---
42	---	---
43	---	---
44	---	---
45	---	---

BODY WEIGHT GAIN (%)
FEMALES

GROUP 3 (50 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
46	0	13	26	42	49	---	---	---
47	0	11	26	37	44	---	---	---
48	0	8	21	30	34	---	---	---
49	0	13	30	41	49	---	---	---
50	0	16	27	40	48	---	---	---

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
46	---	---
47	---	---
48	---	---
49	---	---
50	---	---

BODY WEIGHT GAIN (%)
FEMALES

GROUP 4 (250 MG/KG)

DAYS WEEKS ANIMAL	TREATMENT					RECOVERY		
	1 1	8 2	15 3	22 4	28 4	1 1	8 2	15 3
51	0	14	28	37	38	---	---	---
52	0	13	32	46	49	---	---	---
53	0	12	28	40	41	---	---	---
54	0	19	30	39	40	---	---	---
55	0	11	28	40	45	---	---	---
56	0	9	27	35	38	28	48	58
57	0	14	28	36	39	27	50	55
58	0	10	28	44	45	29	64	69
59	0	15	31	42	49	39	65	72
60	0	11	18	34	34	23	49	61

DAYS WEEKS ANIMAL	RECOVERY	
	22 4	28 4
51	---	---
52	---	---
53	---	---
54	---	---
55	---	---
56	60	61
57	56	65
58	74	79
59	79	81
60	64	69

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 1
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

GROUP 1 (CONTROL)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
1 2	21	21	22	22	24	24	27	41

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

GROUP 2 (5 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
3	21	22	22	23	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 3
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

GROUP 3 (50 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
4	20	22	22	22	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 4
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

GROUP 4 (250 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
5	19	20	18	20	---	27	---	21
6	19	20	19	20	---	24	---	31

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 5
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

GROUP 1 (CONTROL)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
7 8	17 15	18 16	18 16	20 18	---	21	---	20 20 37

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 6
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

GROUP 2 (5 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
9	15	16	16	17	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 7
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

GROUP 3 (50 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
10	15	16	16	18	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

FC-IND - 8
06-DEC-94

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

GROUP 4 (250 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
11	16	17	17	18	---	21	19	18
12	13	15	15	16	---	---	---	28

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

RFC-IND - 1
06-DEC-94

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
MALES

GROUP 1 (CONTROL)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
	1 2	104 108	92 91	82 84	88 91	-- 91	-- 84	-- 77 122

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
MALES

GROUP 2 (5 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
3	102	93	82	87	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

RFC-IND - 3
06-DEC-94

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
MALES

GROUP 3 (50 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
4	103	94	84	86	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

RFC-IND - 4
06-DEC-94

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
MALES

GROUP 4 (250 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
5	102	92	77	87	---	98	---	---
6	100	90	77	83	---	82	72	108

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

RFC-IND - 5
06-DEC-94

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
FEMALES

GROUP 1 (CONTROL)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
	7	114	106	94	107	---	---	---
8	104	99	92	104	110	99	95	179

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
FEMALES

GROUP 2 (5 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
9	108	104	95	102	---	---	---	---

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

RFC-IND - 7
06-DEC-94

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
FEMALES

GROUP 3 (50 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
10	104	100	92	104	---	---	---	---

RELATIVE FOOD CONSUMPTION
(G/KG BODY WEIGHT/DAY)
FEMALES

GROUP 4 (250 MG/KG)

DAYS WEEKS CAGE	TREATMENT				RECOVERY			
	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4	1-8 1/2	8-15 2/3	15-22 3/4	22-28 4
11	109	102	93	102	---	109	---	---
12	96	95	87	92	---	95	86	134

OPHTHALMOSCOPIC EXAMINATIONS
MALES
AT WEEK 4

GROUP 1 (CONTROL)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

1	BOTH	NO FINDINGS
2	BOTH	NO FINDINGS
3	BOTH	NO FINDINGS
4	BOTH	NO FINDINGS
5	LEFT	LENS OPACITY ANTERIOR
6	BOTH	NO FINDINGS
7	BOTH	NO FINDINGS
8	BOTH	NO FINDINGS
9	BOTH	NO FINDINGS
10	RIGHT	LENS OPACITY ANTERIOR

GROUP 2 (5 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

11	BOTH	NO FINDINGS
12	BOTH	NO FINDINGS
13	BOTH	NO FINDINGS
14	BOTH	NO FINDINGS
15	BOTH	NO FINDINGS

GROUP 3 (50 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

16	BOTH	NO FINDINGS
17	BOTH	NO FINDINGS
18	LEFT	LENS OPACITY ANTERIOR
19	BOTH	NO FINDINGS
20	RIGHT	CORNEAL OPACITY

GROUP 4 (250 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

21	BOTH	NO FINDINGS
22	BOTH	NO FINDINGS
23	BOTH	NO FINDINGS
24	RIGHT	LENS OPACITY ANTERIOR
25	BOTH	NO FINDINGS
26	BOTH	NO FINDINGS
27	BOTH	NO FINDINGS
28	BOTH	NO FINDINGS
29	BOTH	NO FINDINGS
30	BOTH	NO FINDINGS

In the case of unilateral findings, the other eye did not show any changes.

OPHTHALMOSCOPIC EXAMINATIONS
FEMALES
AT WEEK 4

GROUP 1 (CONTROL)

ANIMAL	EYE(S)	OBSERVATION
31	BOTH	NO FINDINGS
32	BOTH	NO FINDINGS
33	BOTH	NO FINDINGS
34	BOTH	NO FINDINGS
35	BOTH	NO FINDINGS
36	RIGHT	LENS OPACITY ANTERIOR
37	BOTH	NO FINDINGS
38	BOTH	NO FINDINGS
39	BOTH	NO FINDINGS
40	BOTH	NO FINDINGS

GROUP 2 (5 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
41	BOTH	NO FINDINGS
42	BOTH	NO FINDINGS
43	BOTH	NO FINDINGS
44	BOTH	NO FINDINGS
45	BOTH	NO FINDINGS

GROUP 3 (50 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
46	BOTH	NO FINDINGS
47	BOTH	NO FINDINGS
48	BOTH	NO FINDINGS
49	BOTH	NO FINDINGS
50	LEFT	LENS OPACITY ANTERIOR

GROUP 4 (250 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
51	BOTH	NO FINDINGS
52	BOTH	NO FINDINGS
53	BOTH	LENS OPACITY ANTERIOR
54	BOTH	NO FINDINGS
55	BOTH	NO FINDINGS
56	BOTH	NO FINDINGS
57	BOTH	NO FINDINGS
58	BOTH	NO FINDINGS
59	RIGHT	CHROMODACRYORRHEA
60	BOTH	NO FINDINGS

In the case of unilateral findings, the other eye did not show any changes.

OPHTHALMOSCOPIC EXAMINATIONS
MALES
AT WEEK 8

GROUP 1 (CONTROL)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

6	BOTH	NO FINDINGS
7	BOTH	NO FINDINGS
8	BOTH	NO FINDINGS
9	BOTH	NO FINDINGS
10	BOTH	NO FINDINGS

GROUP 4 (250 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

26	LEFT	CHROMODACRYORRHEA
27	BOTH	NO FINDINGS
28	BOTH	NO FINDINGS
29	BOTH	NO FINDINGS
30	BOTH	NO FINDINGS

In the case of unilateral findings, the other eye did not show any changes.

OPHTHALMOSCOPIC EXAMINATIONS
FEMALES
AT WEEK 8

GROUP 1 (CONTROL)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

36	BOTH	NO FINDINGS
37	BOTH	NO FINDINGS
38	BOTH	NO FINDINGS
39	BOTH	NO FINDINGS
40	BOTH	NO FINDINGS

GROUP 4 (250 MG/KG)

ANIMAL	EYE(S)	OBSERVATION
--------	--------	-------------

56	BOTH	NO FINDINGS
57	BOTH	NO FINDINGS
58	BOTH	NO FINDINGS
59	BOTH	NO FINDINGS
60	BOTH	NO FINDINGS



**HAEMATOLOGY
AFTER 4 WEEKS
MALES
GROUP 1 (CONTROL)**

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
1	7.35	9.1	0.415	56.5	1.2	21.9	11.3	5.2
2	7.02	9.2	0.414	59.0	1.3	22.2	10.9	7.1
3	7.94	9.7	0.432	54.4	1.2	22.5	11.9	9.9
4	7.99	9.7	0.441	55.2	1.2	22.0	12.1	6.4
5	7.37	9.1	0.405	55.0	1.2	22.5	12.1	6.3
6	7.65	9.4	0.420	54.9	1.2	22.4	12.9	7.6
7	7.11	8.9	0.405	57.0	1.3	22.0	11.5	5.5
8	7.27	9.1	0.409	56.3	1.3	22.2	11.7	5.0
9	7.12	8.7	0.395	55.5	1.2	22.0	11.7	4.7
10	8.02	10.2	0.456	56.9	1.3	22.4	11.1	4.7

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
1	0.050	0.020	0.000	0.045	0.885	742	15.4	14.8
2	0.045	0.000	0.000	0.005	0.950	869	14.8	18.3
3	0.045	0.005	0.000	0.015	0.935	950	15.0	15.2
4	0.100	0.000	0.000	0.035	0.865	955	15.3	14.6
5	0.055	0.010	0.000	0.010	0.925	920	13.9	16.3
6	0.100	0.010	0.000	0.005	0.885	898	15.2	---
7	0.095	0.000	0.000	0.010	0.895	1030	---	---
8	0.060	0.000	0.000	0.040	0.900	867	15.5	17.4
9	0.045	0.000	0.000	0.020	0.935	905	15.2	16.1
10	0.130	0.010	0.000	0.010	0.850	845	12.6	18.3

animal 6 --- technical error
animal 7 --- sample clotted

HAEMATOLOGY
AFTER 4 WEEKS
MALES
GROUP 2 (5 MG/KG)

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV fl	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
11	7.43	9.2	0.414	55.7	1.2	22.2	11.7	5.0
12	7.82	9.7	0.444	56.8	1.2	21.8	11.2	6.1
13	8.26	9.9	0.446	54.0	1.2	22.2	12.4	6.8
14	7.22	9.4	0.422	58.4	1.3	22.3	11.0	5.3
15	7.73	9.6	0.429	55.5	1.2	22.4	11.3	4.1

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
11	0.060	0.005	0.000	0.000	0.935	836	15.1	16.3
12	0.105	0.000	0.000	0.020	0.875	801	15.2	17.0
13	0.105	0.000	0.000	0.020	0.875	890	13.7	18.7
14	0.060	0.000	0.000	0.010	0.930	844	13.6	17.6
15	0.050	0.005	0.000	0.005	0.940	822	14.8	17.3

**HAEMATOLOGY
AFTER 4 WEEKS
MALES
GROUP 3 (50 MG/KG)**

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
16	7.86	9.7	0.444	56.5	1.2	21.8	11.3	4.6
17	7.06	8.9	0.396	56.1	1.3	22.5	12.0	7.0
18	8.20	9.6	0.439	53.5	1.2	21.9	12.7	6.5
19	6.88	9.1	0.399	58.0	1.3	22.8	11.4	4.5
20	6.95	9.1	0.405	58.3	1.3	22.5	11.6	6.1

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
16	0.080	0.005	0.000	0.020	0.895	814	14.0	15.7
17	0.090	0.000	0.000	0.040	0.870	900	---	---
18	0.100	0.010	0.000	0.015	0.875	958	14.4	17.3
19	0.135	0.000	0.000	0.015	0.850	967	14.4	16.6
20	0.175	0.005	0.000	0.015	0.805	957	15.5	16.1

--- unreliable value as result of to high sample volume

HAEMATOLOGY
AFTER 4 WEEKS
MALES
GROUP 4 (250 MG/KG)

HAEMATOLOGY PARAMETERS

ANIMAL NUMBER	RBC T/1	Hb mmol/l	HCT 1/l	MCV fl	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
21	6.48	8.1	0.362	55.9	1.3	22.4	12.4	7.6
22	6.70	8.4	0.369	55.1	1.3	22.8	14.1	6.8
23	6.88	7.9	0.353	51.3	1.1	22.4	13.8	5.3
24	7.32	8.8	0.384	52.5	1.2	22.9	12.5	6.4
25	6.36	7.6	0.338	53.1	1.2	22.5	13.4	5.7
26	7.33	8.6	0.393	53.6	1.2	21.9	13.0	5.4
27	7.02	8.7	0.376	53.6	1.2	23.1	12.5	5.3
28	6.45	8.2	0.369	57.2	1.3	22.2	11.3	3.8
29	6.77	8.4	0.374	55.2	1.2	22.5	12.7	5.9
30	7.68	9.1	0.408	53.1	1.2	22.3	14.2	6.4

HAEMATOLOGY PARAMETERS

ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
21	0.150	0.010	0.000	0.015	0.825	1069	14.0	14.5
22	0.115	0.000	0.000	0.010	0.875	982	14.5	15.4
23	0.175	0.005	0.000	0.005	0.815	996	12.9	18.4
24	0.115	0.000	0.000	0.005	0.880	1020	13.1	16.8
25	0.125	0.005	0.000	0.010	0.860	978	13.9	13.9
26	0.650	0.000	0.000	0.015	0.335	937	13.3	28.4
27	0.350	0.020	0.000	0.030	0.600	1123	12.9	17.4
28	0.325	0.010	0.000	0.010	0.655	841	13.3	20.9
29	0.275	0.010	0.000	0.020	0.695	1019	13.4	22.2
30	0.135	0.010	0.000	0.050	0.805	917	14.0	15.8

HAEMATOLOGY
AFTER 4 WEEKS
FEMALES
GROUP 1 (CONTROL)

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
31	7.72	9.6	0.435	56.3	1.2	22.1	10.7	3.4
32	6.94	8.6	0.384	55.3	1.2	22.4	12.1	2.6
33	6.87	8.6	0.382	55.6	1.3	22.5	11.0	3.0
34	6.70	8.6	0.384	57.3	1.3	22.4	11.2	2.8
35	6.70	8.5	0.387	57.8	1.3	22.0	10.7	2.6
36	6.93	8.6	0.392	56.6	1.2	21.9	11.0	4.0
37	7.21	8.6	0.390	54.1	1.2	22.1	12.1	2.0
38	7.13	9.2	0.411	57.6	1.3	22.4	10.9	3.4
39	6.94	8.5	0.382	55.0	1.2	22.3	10.9	4.8
40	7.41	8.9	0.407	54.9	1.2	21.9	11.8	2.9

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
31	0.085	0.000	0.000	0.005	0.910	817	15.5	19.9
32	0.115	0.010	0.000	0.010	0.865	898	16.0	19.5
33	0.130	0.010	0.000	0.020	0.840	821	16.3	19.3
34	0.205	0.025	0.000	0.015	0.755	768	15.8	18.1
35	0.095	0.005	0.000	0.005	0.895	749	16.4	17.7
36	0.145	0.005	0.000	0.020	0.830	755	---	---
37	0.140	0.005	0.000	0.010	0.845	1027	15.6	18.2
38	0.115	0.010	0.000	0.010	0.865	883	14.6	13.7
39	0.065	0.005	0.000	0.010	0.920	790	16.4	16.4
40	0.050	0.010	0.000	0.015	0.925	872	16.6	17.3

--- sample clotted

**HAEMATOLOGY
AFTER 4 WEEKS
FEMALES
GROUP 2 (5 MG/KG)**

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
41	7.12	8.7	0.398	55.9	1.2	21.9	10.6	2.8
42	6.80	8.6	0.387	56.9	1.3	22.2	10.6	2.0
43	6.86	9.2	0.394	57.4	1.3	23.4	10.6	4.2
44	6.86	8.9	0.395	57.6	1.3	22.5	10.8	2.9
45	7.33	8.7	0.385	52.5	1.2	22.6	11.2	2.5

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
41	0.085	0.030	0.000	0.030	0.855	804	15.4	24.8
42	0.055	0.010	0.000	0.025	0.910	871	16.8	18.0
43	0.070	0.010	0.000	0.000	0.920	803	---	---
44	0.090	0.020	0.000	0.005	0.885	801	16.1	19.8
45	0.090	0.000	0.000	0.010	0.900	919	15.8	17.4

--- sample clotted

HAEMATOLOGY
AFTER 4 WEEKS
FEMALES
GROUP 3 (50 MG/KG)

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
46	7.23	9.0	0.407	56.3	1.2	22.1	10.7	6.0
47	7.18	8.8	0.386	53.8	1.2	22.8	11.4	2.5
48	6.72	8.4	0.373	55.5	1.3	22.5	11.4	3.2
49	7.48	9.1	0.417	55.7	1.2	21.8	11.2	3.8
50	6.58	8.5	0.381	57.9	1.3	22.3	10.4	3.5

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
46	0.075	0.020	0.000	0.010	0.895	1049	15.0	16.2
47	0.125	0.005	0.000	0.020	0.850	886	15.5	17.7
48	0.065	0.010	0.000	0.025	0.900	890	14.7	18.4
49	0.090	0.000	0.000	0.020	0.890	766	15.6	17.7
50	0.130	0.020	0.000	0.005	0.845	846	15.3	18.0

**HAEMATOLOGY
AFTER 4 WEEKS
FEMALES
GROUP 4 (250 MG/KG)**

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/1	HB mmol/l	HCT 1/l	MCV fl	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
51	---	---	---	---	---	---	---	---
52	6.64	8.1	0.360	54.2	1.2	22.5	11.8	5.1
53	6.87	8.6	0.386	56.2	1.3	22.3	11.6	3.2
54	6.82	8.6	0.387	56.7	1.3	22.2	10.6	2.5
55	5.99	7.3	0.327	54.6	1.2	22.3	11.2	2.4
56	6.75	8.3	0.369	54.7	1.2	22.5	12.1	3.6
57	6.29	7.7	0.347	55.2	1.2	22.2	12.6	3.6
58	6.79	8.3	0.362	53.3	1.2	22.9	12.0	6.4
59	6.73	8.6	0.378	56.2	1.3	22.8	11.2	3.9
60	6.45	8.1	0.353	54.7	1.3	22.9	12.2	3.9

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
51	---	---	---	---	---	---	15.3	17.0
52	0.050	0.010	0.000	0.005	0.935	972	15.6	15.5
53	0.110	0.010	0.000	0.020	0.860	745	15.3	15.9
54	0.165	0.005	0.000	0.020	0.810	1089	15.4	14.1
55	0.255	0.000	0.000	0.010	0.735	1019	16.2	21.7
56	0.140	0.020	0.000	0.005	0.835	999	15.3	17.8
57	0.195	0.010	0.000	0.015	0.780	974	15.4	16.3
58	0.290	0.015	0.000	0.010	0.685	1213	14.7	15.8
59	0.300	0.005	0.000	0.035	0.660	993	14.8	15.4
60	0.143	0.010	0.000	0.005	0.840	901	15.4	17.1

--- sample partly clotted

HAEMATOLOGY
AFTER 8 WEEKS
MALES
GROUP 1 (CONTROL)

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
6	8.43	10.3	0.441	52.3	1.2	23.4	14.5	8.7
7	7.80	10.3	0.431	55.3	1.3	23.9	13.8	8.2
8	8.21	10.2	0.445	54.2	1.2	22.9	14.3	6.4
9	7.76	9.9	0.428	55.2	1.3	23.1	14.7	6.0
10	8.36	10.8	0.460	55.0	1.3	23.5	13.8	5.9

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
6	0.140	0.000	0.000	0.025	0.835	825	14.5	17.7
7	0.110	0.000	0.000	0.045	0.845	931	12.5	15.6
8	0.100	0.015	0.000	0.010	0.875	817	14.5	16.9
9	0.090	0.000	0.000	0.010	0.900	841	12.8	16.5
10	0.105	0.015	0.000	0.010	0.870	912	13.9	17.2

**HAEMATOLOGY
AFTER 8 WEEKS
MALES
GROUP 4 (250 MG/KG)**

HAEMATOLOGY PARAMETERS

ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV fl	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
26	8.08	10.3	0.449	55.6	1.3	22.9	17.1	6.3
27	8.30	10.5	0.454	54.7	1.3	23.1	14.3	4.7
28	8.00	10.5	0.453	56.6	1.3	23.2	12.8	5.1
29	7.55	10.2	0.426	56.4	1.4	23.9	13.5	5.6
30	8.39	10.5	0.461	54.9	1.3	22.8	14.6	6.5

HAEMATOLOGY PARAMETERS

ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
26	0.265	0.010	0.000	0.025	0.700	1049	14.1	15.8
27	0.130	0.005	0.000	0.000	0.865	1030	13.4	18.5
28	0.140	0.020	0.000	0.015	0.825	871	14.7	18.5
29	0.290	0.000	0.000	0.025	0.685	903	13.7	15.8
30	0.100	0.000	0.000	0.015	0.885	771	12.8	17.9

**HAEMATOLOGY
AFTER 8 WEEKS
FEMALES
GROUP 1 (CONTROL)**

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV fl	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
36	7.00	9.7	0.414	59.1	1.4	23.4	13.4	4.8
37	7.02	9.2	0.389	55.4	1.3	23.7	14.1	--
38	7.14	10.2	0.423	59.2	1.4	24.1	12.8	4.5
39	7.19	9.5	0.406	56.5	1.3	23.4	12.0	5.9
40	7.36	9.7	0.414	56.3	1.3	23.4	13.1	4.3

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
36	0.100	0.005	0.000	0.005	0.890	771	14.1	17.7
37	0.200	0.015	0.000	0.005	0.780	845	15.6	17.0
38	0.075	0.000	0.000	0.005	0.920	787	14.0	15.3
39	0.090	0.000	0.000	0.000	0.910	695	14.9	15.0
40	0.070	0.010	0.000	0.015	0.905	797	15.0	15.4

--- technical error

**HAEMATOLOGY
 AFTER 8 WEEKS
 FEMALES
 GROUP 4 (250 MG/KG)**

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	RBC T/l	HB mmol/l	HCT 1/l	MCV f1	MCH fmol	MCHC mmol/l	RDW %	WBC G/l
56	7.35	9.5	0.406	55.2	1.3	23.4	12.9	4.3
57	7.29	9.6	0.416	57.1	1.3	23.1	12.8	4.3
58	7.49	9.8	0.413	55.1	1.3	23.7	13.5	5.5
59	7.07	9.6	0.415	58.7	1.4	23.1	13.0	4.0
60	7.06	9.7	0.409	57.9	1.4	23.7	12.9	4.6

HAEMATOLOGY PARAMETERS								
ANIMAL NUMBER	SEG. 1	EO. 1	BASO. 1	MONO. 1	LYMPH. 1	PLATELETS G/l	PT SEC	PTT SEC
56	0.155	0.015	0.000	0.020	0.810	836	---	---
57	0.210	0.005	0.000	0.015	0.770	926	14.5	14.5
58	0.180	0.020	0.000	0.005	0.795	891	14.6	14.1
59	0.150	0.010	0.000	0.005	0.835	759	13.0	16.1
60	0.175	0.015	0.000	0.030	0.780	817	12.8	17.4

--- sample clotted

**CLINICAL BIOCHEMISTRY
 AFTER 4 WEEKS
 MALES
 GROUP 1 (CONTROL)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
1	0.62	1.86	3	2.48	0.42	33.0	4.76	5.1
2	0.74	2.01	2	2.00	0.88	33.0	6.97	4.8
3	0.71	1.56	3	2.07	1.06	33.0	7.12	6.1
4	0.77	1.53	2	2.04	0.69	36.0	8.94	5.1
5	0.77	1.59	2	2.36	0.58	38.0	7.20	6.6
6	0.58	2.07	2	1.91	0.71	35.0	8.88	5.5
7	0.73	1.84	2	2.13	0.52	37.0	8.33	5.4
8	0.70	1.74	2	2.02	1.32	37.0	7.42	5.3
9	0.78	2.03	2	2.10	0.68	40.0	4.44	7.1
10	0.61	1.72	2	2.37	0.42	40.0	6.31	5.4

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
1	61	32	29	1	5.13	142.0	4.74	96
2	62	32	30	1	6.32	142.0	3.92	97
3	67	34	33	1	4.87	141.7	4.05	95
4	64	34	30	1	6.68	142.0	4.71	94
5	65	34	31	1	6.12	141.6	4.57	93
6	61	31	30	1	5.31	140.8	4.69	95
7	65	35	30	1	5.23	141.6	4.49	100
8	59	32	27	1	8.17	140.7	4.27	97
9	62	34	28	1	7.42	142.3	3.96	98
10	62	32	30	1	6.40	136.0	3.78	96

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
1	2.61	2.81
2	2.56	2.33
3	2.65	2.51
4	2.72	2.73
5	2.65	2.56
6	2.51	2.53
7	2.60	2.46
8	2.49	2.35
9	2.58	2.59
10	2.45	2.37

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
MALES
GROUP 2 (5 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
11	0.66	1.62	2	2.17	0.85	35.0	5.92	6.8
12	0.79	1.72	2	1.99	0.44	40.0	4.76	6.5
13	0.72	1.57	2	2.20	1.35	30.0	6.51	5.7
14	0.60	1.73	3	2.42	0.58	38.0	6.18	4.9
15	0.73	1.84	2	2.00	0.51	37.0	6.03	6.5

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
11	61	31	30	1	4.79	143.7	4.31	97
12	59	32	27	1	5.26	143.4	5.20	101
13	63	33	30	1	5.55	141.8	4.42	94
14	64	33	31	1	6.27	142.9	4.22	99
15	62	34	28	1	6.99	141.0	4.59	98

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
11	2.64	2.43
12	2.57	2.64
13	2.60	2.23
14	2.57	2.15
15	2.59	2.47

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
MALES
GROUP 3 (50 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
16	0.57	1.63	2	2.32	0.92	39.0	6.67	5.3
17	0.63	1.73	3	2.04	0.92	42.0	5.61	5.3
18	0.53	1.68	3	2.29	0.84	39.0	6.26	5.4
19	0.65	1.88	2	2.55	0.46	42.0	5.15	5.4
20	0.87	1.55	2	2.10	0.78	42.0	5.37	5.5

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
16	61	31	30	1	7.12	142.7	4.15	97
17	61	31	30	1	4.50	141.5	4.57	95
18	61	33	28	1	7.26	141.8	4.29	96
19	63	31	32	1	4.16	142.1	3.86	96
20	63	31	32	1	5.01	140.9	3.91	93

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
16	2.55	2.63
17	2.50	2.44
18	2.60	2.50
19	2.47	2.25
20	2.50	2.63

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
MALES
GROUP 4 (250 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILIRUBIN T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
21	0.90	1.57	2	2.49	1.42	46.0	3.97	10.0
22	0.81	2.07	2	1.94	0.84	41.0	4.08	6.4
23	1.08	1.84	2	2.22	0.72	38.0	5.08	7.5
24	0.79	1.67	2	2.89	0.70	45.0	5.18	9.2
25	0.66	1.59	1	2.59	2.13	37.0	5.25	9.3
26	1.75	5.85	2	1.49	1.31	50.0	7.82	10.5
27	1.15	1.75	---	2.31	4.50	43.0	5.25	9.4
28	0.52	1.53	2	1.81	1.31	52.0	7.34	10.4
29	0.93	1.32	2	2.57	1.30	38.0	6.15	6.9
30	0.88	1.41	2	2.46	2.18	42.0	5.49	6.7

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
21	53	27	26	1	4.25	141.6	4.76	94
22	56	30	26	1	4.80	141.2	3.70	94
23	53	29	24	1	3.30	137.5	4.13	91
24	61	31	30	1	4.77	140.3	3.87	91
25	52	29	23	1	4.20	141.2	4.69	95
26	47	26	21	1	4.34	136.4	4.51	89
27	54	30	24	1	3.99	141.5	4.22	96
28	52	27	25	1	4.59	142.8	4.22	93
29	58	30	28	1	8.93	141.8	3.89	90
30	59	32	27	1	5.83	142.1	3.79	95

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
21	2.56	3.75
22	2.49	3.06
23	2.40	2.56
24	2.59	3.12
25	2.49	3.29
26	2.34	3.43
27	2.58	3.58
28	2.43	3.20
29	2.61	3.00
30	2.75	2.93

Note: serum samples were (slightly) lipemic. Total bilirubin value for animal 27 not reliable.

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
FEMALES
GROUP 1 (CONTROL)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
31	0.53	1.75	3	1.24	0.26	31.0	5.24	7.1
32	0.68	1.58	2	1.48	0.38	35.0	5.75	6.1
33	0.48	1.64	3	1.40	0.40	38.0	4.85	7.0
34	0.41	1.53	3	2.03	0.48	36.0	5.38	6.9
35	0.65	1.71	3	1.49	0.53	46.0	5.44	11.9
36	0.56	1.77	3	1.20	0.34	39.0	5.36	7.2
37	0.47	1.56	3	1.72	0.51	32.0	5.47	7.0
38	0.66	1.31	4	2.24	0.56	27.0	5.16	7.0
39	0.51	1.58	3	1.18	0.59	35.0	5.50	5.7
40	0.56	1.54	2	2.27	0.42	33.0	5.01	5.8

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
31	60	33	27	1	3.45	140.1	4.21	99
32	64	34	30	1	2.41	138.9	3.71	98
33	65	36	29	1	3.47	140.4	4.17	101
34	65	37	28	1	2.57	139.7	3.93	100
35	55	32	23	1	3.21	139.0	3.99	99
36	65	33	32	1	4.31	143.0	3.81	101
37	60	33	27	1	2.93	140.5	4.02	98
38	61	33	28	1	2.67	140.3	4.93	100
39	60	32	28	1	2.49	140.3	4.61	99
40	64	33	31	1	4.66	140.3	4.05	99

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
31	2.45	2.00
32	2.40	1.67
33	2.50	1.83
34	2.39	1.47
35	2.48	2.25
36	2.63	1.81
37	2.53	2.03
38	2.59	2.58
39	2.45	2.11
40	2.55	1.78

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
FEMALES
GROUP 2 (5 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
41	0.59	1.71	3	1.38	0.35	43.0	5.16	6.3
42	0.46	1.53	3	1.08	0.36	32.0	5.92	5.5
43	0.82	1.99	2	2.01	0.34	44.0	5.21	9.1
44	0.49	1.62	2	1.90	0.42	33.0	5.26	6.1
45	0.40	1.47	2	1.30	0.31	38.0	5.14	7.3

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
41	63	34	29	1	2.63	142.4	4.11	99
42	58	33	25	1	4.06	141.6	4.26	100
43	63	34	29	1	3.12	142.5	3.84	101
44	62	32	30	1	2.99	143.1	3.97	104
45	60	34	26	1	2.32	139.9	4.39	99

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
41	2.50	2.04
42	2.46	1.94
43	2.50	1.77
44	2.41	1.46
45	2.47	1.74

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
FEMALES
GROUP 3 (50 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
46	0.51	1.82	3	1.55	1.52	33.0	6.60	8.3
47	0.39	1.79	3	1.96	0.39	32.0	4.86	6.3
48	0.56	1.54	3	1.38	0.44	33.0	4.94	6.7
49	0.43	1.48	5	1.32	0.30	37.0	5.47	7.0
50	0.53	1.32	3	1.83	0.82	38.0	5.81	5.3

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
46	62	34	28	1	3.31	141.8	4.08	95
47	64	36	28	1	3.08	140.3	4.07	101
48	61	36	25	1	2.84	141.0	4.21	99
49	64	35	29	1	2.10	140.7	3.91	98
50	67	36	31	1	2.22	143.3	3.73	104

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
46	2.67	2.33
47	2.52	2.07
48	2.43	2.06
49	2.52	2.19
50	2.65	1.80

**CLINICAL BIOCHEMISTRY
AFTER 4 WEEKS
FEMALES
GROUP 4 (250 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
51	0.54	1.92	3	1.96	0.80	36.0	4.96	7.5
52	0.66	1.58	1	2.24	2.68	30.0	4.94	5.3
53	0.79	1.62	3	2.37	0.63	34.0	5.83	6.1
54	0.67	1.65	2	1.58	0.69	34.0	5.17	5.6
55	1.58	10.43	2	1.38	0.70	43.0	5.09	12.5
56	0.59	1.42	1	2.02	2.56	33.0	3.56	5.9
57	0.44	1.77	2	1.96	2.87	41.0	4.51	9.5
58	0.80	1.59	3	1.99	1.16	62.0	6.13	13.6
59	0.78	1.32	2	2.02	0.69	37.0	5.75	6.3
60	0.66	1.37	3	2.20	1.38	45.0	4.03	8.9

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
51	55	32	23	1	2.27	138.9	3.61	94
52	57	31	26	1	2.88	139.5	4.00	100
53	62	34	28	1	3.18	141.9	3.91	97
54	63	35	28	1	3.43	142.2	3.55	101
55	51	30	21	1	3.00	140.5	3.97	96
56	62	34	28	1	2.26	142.6	4.14	95
57	55	31	24	1	4.56	143.0	3.58	99
58	62	31	31	1	3.26	141.5	3.97	91
59	55	32	23	1	3.06	143.0	3.84	98
60	58	32	26	1	3.51	143.6	3.93	100

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
51	2.53	2.06
52	2.50	2.16
53	2.52	2.52
54	2.53	1.43
55	2.49	2.55
56	2.67	2.30
57	2.53	2.23
58	2.54	2.86
59	2.48	2.04
60	2.52	2.74

Note: serum samples were (slightly) lipemic.

CLINICAL BIOCHEMISTRY
AFTER 8 WEEKS
MALES
GROUP 1 (CONTROL)

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
6	0.57	1.66	2	1.68	1.43	34.0	7.13	6.9
7	0.61	1.60	2	2.39	1.05	35.0	7.47	6.8
8	0.54	1.55	2	1.68	2.56	39.0	8.10	6.0
9	0.64	1.73	4	1.94	0.78	40.0	7.01	9.0
10	0.55	1.59	2	1.99	0.87	42.0	7.32	8.7

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
6	65	32	33	1	3.31	142.6	4.35	99
7	64	30	34	1	2.49	142.8	5.10	101
8	64	32	32	1	5.10	142.8	4.23	102
9	66	32	34	1	4.38	141.8	3.93	99
10	63	30	33	1	3.80	140.7	4.46	99

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
6	2.52	2.33
7	2.55	2.02
8	2.53	2.17
9	2.48	2.15
10	2.51	2.07

**CLINICAL BIOCHEMISTRY
 AFTER 8 WEEKS
 MALES
 GROUP 4 (250 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
26	0.65	2.14	2	1.62	0.64	37.0	6.58	6.1
27	0.42	1.49	2	1.72	0.56	35.0	7.66	7.3
28	0.35	1.85	1	1.28	1.31	39.0	6.30	6.8
29	0.54	1.80	2	2.14	1.21	34.0	7.45	7.0
30	0.60	1.88	2	1.73	0.97	36.0	7.87	7.6

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
26	72	32	40	1	3.75	139.8	4.35	101
27	71	34	37	1	2.57	144.2	4.91	99
28	66	29	37	1	2.46	142.6	4.42	98
29	65	32	33	1	4.22	139.1	4.76	98
30	68	32	36	1	4.61	142.5	4.36	98

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
26	2.40	2.05
27	2.55	2.00
28	2.44	2.05
29	2.47	2.41
30	2.43	2.30

CLINICAL BIOCHEMISTRY
AFTER 8 WEEKS
FEMALES
GROUP 1 (CONTROL)

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
36	0.59	1.49	2	1.18	0.34	43.0	6.32	9.3
37	0.38	1.44	3	1.75	0.41	41.0	6.63	8.0
38	0.49	1.10	2	2.34	0.68	32.0	5.66	7.4
39	0.55	1.47	2	1.39	0.32	38.0	6.21	6.0
40	0.45	1.51	2	2.18	0.50	39.0	5.92	6.7

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
36	69	33	36	1	2.35	138.0	3.76	101
37	62	32	30	1	1.66	136.3	3.85	100
38	70	35	35	1	1.33	137.1	3.99	98
39	66	34	32	1	1.78	138.6	3.66	97
40	64	33	31	1	2.85	141.4	4.21	101

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
36	2.57	1.74
37	2.36	1.87
38	2.51	2.24
39	2.36	1.40
40	2.49	1.78

**CLINICAL BIOCHEMISTRY
 AFTER 8 WEEKS
 FEMALES
 GROUP 4 (250 MG/KG)**

ANIMAL NUMBER	ALAT(GPT) ukat/l	ASAT(GOT) ukat/l	BILI T. umol/l	CHOLEST.T. mmol/l	TRIGL. mmol/l	CREATININE umol/l	GLUCOSE mmol/l	UREA mmol/l
56	0.34	1.20	2	1.64	0.85	38.0	5.74	6.7
57	0.44	1.72	2	1.41	1.39	37.0	3.60	9.0
58	0.55	1.62	2	1.87	0.52	59.0	6.49	11.0
59	0.45	1.22	2	2.09	0.47	46.0	7.82	8.4
60	0.46	1.49	2	2.58	0.43	37.0	5.40	7.8

ANIMAL NUMBER	PROTEIN T. g/l	ALBUMIN g/l	GLOBULIN g/l	A/G RATIO	ALP ukat/l	SODIUM mmol/l	POTASSIUM mmol/l	CHLORIDE mmol/l
56	70	34	36	1	1.16	139.3	3.72	102
57	68	34	34	1	1.83	142.6	4.31	100
58	70	34	36	1	2.09	140.1	3.87	96
59	66	31	35	1	1.73	140.9	3.90	100
60	69	34	35	1	1.50	140.6	4.06	101

ANIMAL NUMBER	CALCIUM mmol/l	INORG PHOS mmol/l
56	2.46	1.40
57	2.49	1.92
58	2.51	1.66
59	2.35	1.57
60	2.46	1.73

**MACROSCOPIC FINDINGS
MALES
GROUP 1 (CONTROL)**

ANIMAL 1

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 2

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 3

(SCHEDULED NECROPSY, 31-AUG-94)

KIDNEYS..... RIGHT SIDE: PELVIC DILATION.

ANIMAL 4

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 5

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 6

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 7

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 8

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 9

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 10

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MAC-IND - 2
06-OCT-94

**MACROSCOPIC FINDINGS
MALES
GROUP 2 (5 MG/KG)**

ANIMAL 11

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 12

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 13

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 14

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 15

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MAC-IND - 3
06-OCT-94

**MACROSCOPIC FINDINGS
MALES
GROUP 3 (50 MG/KG)**

ANIMAL 16

(SCHEDULED NECROPSY, 31-AUG-94)

KIDNEYS..... DISCOLOURATION, PALE.

ANIMAL 17

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 18

(SCHEDULED NECROPSY, 31-AUG-94)

KIDNEYS..... ENLARGED, DISCOLOURATION, PALE.

ANIMAL 19

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED.

KIDNEYS..... ENLARGED, DISCOLOURATION, PALE.

ANIMAL 20

(SCHEDULED NECROPSY, 31-AUG-94)

KIDNEYS..... DISCOLOURATION, PALE.

**MACROSCOPIC FINDINGS
MALES
GROUP 4 (250 MG/KG)**

ANIMAL 21

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED.
KIDNEYS..... ENLARGED, DISCOLOURATION, PALE.

ANIMAL 22

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED.

ANIMAL 23

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED.
KIDNEYS..... ENLARGED, DISCOLOURATION, PALE.

ANIMAL 24

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED.
KIDNEYS..... ENLARGED, DISCOLOURATION, PALE.

ANIMAL 25

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.
KIDNEYS..... ENLARGED, DISCOLOURATION, PALE.

ANIMAL 26

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, LEFT UPPER INCISOR MISSING.

ANIMAL 27

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.

ANIMAL 28

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, UPPER INCISORS MISSING.

ANIMAL 29

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE AND OVERGROWTH.

ANIMAL 30

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.

**MACROSCOPIC FINDINGS
FEMALES
GROUP 1 (CONTROL)**

ANIMAL 31

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 32

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 33

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 34

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 35

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 36

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 37

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 38

(SCHEDULED NECROPSY, 28-SEP-94)

LIVER..... LEFT MEDIAN LOBE: DIAPHRAGMATIC HERNIA.

SKIN..... CHEEK REGION, LEFT SIDE: ALOPECIA.

ANIMAL 39

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 40

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

MAC-IND - 6
06-OCT-94

**MACROSCOPIC FINDINGS
FEMALES
GROUP 2 (5 MG/KG)**

ANIMAL 41

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 42

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 43

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 44

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

ANIMAL 45

(SCHEDULED NECROPSY, 31-AUG-94)

NO FINDINGS NOTED

**MACROSCOPIC FINDINGS
FEMALES
GROUP 3 (50 MG/KG)**

ANIMAL 46

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 47

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 48

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 49

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED.

ANIMAL 50

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

**MACROSCOPIC FINDINGS
FEMALES
GROUP 4 (250 MG/KG)**

ANIMAL 51

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 52

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 53

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... LIMITING RIDGE: THICKENED.

ANIMAL 54

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 55

(SCHEDULED NECROPSY, 31-AUG-94)

STOMACH..... GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE: THICKENED.

ANIMAL 56

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.

ANIMAL 57

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.

ANIMAL 58

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.

STOMACH..... LIMITING RIDGE: THICKENED.

KIDNEYS..... IRREGULAR SURFACE.

OVARIES..... LEFT SIDE: WATERY CYST.

ANIMAL 59

(SCHEDULED NECROPSY, 28-SEP-94)

NO FINDINGS NOTED

ANIMAL 60

(SCHEDULED NECROPSY, 28-SEP-94)

ORAL CAVITY..... JAW(S): INCISORS WHITE.

**ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
MALES**

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
1	269	1.95	1.001	7.88	1.68	0.050	0.602	3.01
2	260	1.92	0.868	7.60	1.73	0.049	0.520	3.26
3	288	1.94	1.004	9.86	1.70	0.049	0.556	3.37
4	254	1.79	0.926	8.21	1.65	0.063	0.611	3.41
5	276	1.81	0.845	8.24	1.73	0.042	0.620	3.24

GROUP 2 (5 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
11	280	1.91	0.963	8.76	1.86	0.070	0.618	3.90
12	239	1.82	0.803	6.47	1.71	0.046	0.511	3.06
13	267	2.01	0.868	8.17	2.02	0.069	0.725	3.24
14	259	1.93	1.065	7.35	1.78	0.061	0.516	3.33
15	266	1.84	0.911	7.30	1.73	0.053	0.453	3.19

GROUP 3 (50 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
16	242	1.78	0.907	7.66	1.86	0.059	0.479	3.23
17	243	1.77	0.821	7.44	1.76	0.054	0.380	2.94
18	227	1.76	0.855	7.13	2.18	0.063	0.460	3.23
19	261	1.97	0.929	8.14	2.17	0.084	0.543	3.04
20	294	1.96	0.917	9.60	2.45	0.070	0.712	3.57

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
21	238	1.88	0.828	10.68	4.65	0.074	0.617	2.99
22	209	1.96	0.686	7.21	2.08	0.054	0.441	2.89
23	226	1.81	0.782	10.19	2.86	0.082	0.457	3.61
24	199	1.90	0.822	8.13	2.40	0.070	0.455	2.81
25	238	1.90	0.814	10.48	3.35	0.077	0.520	3.22

**ORGAN/BODY WEIGHT RATIOS (%)
AFTER 4 WEEKS
MALES**

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
1	269	0.72	0.372	2.93	0.63	0.019	0.224	1.12
2	260	0.74	0.334	2.92	0.66	0.019	0.200	1.25
3	288	0.67	0.349	3.42	0.59	0.017	0.193	1.17
4	254	0.70	0.365	3.23	0.65	0.025	0.241	1.34
5	276	0.66	0.306	2.99	0.63	0.015	0.225	1.18

GROUP 2 (5 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
11	280	0.68	0.344	3.13	0.67	0.025	0.221	1.39
12	239	0.76	0.336	2.71	0.72	0.019	0.214	1.28
13	267	0.75	0.325	3.06	0.76	0.026	0.272	1.21
14	259	0.75	0.411	2.84	0.69	0.024	0.199	1.28
15	266	0.69	0.342	2.74	0.65	0.020	0.170	1.20

GROUP 3 (50 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
16	242	0.74	0.375	3.17	0.77	0.024	0.198	1.34
17	243	0.73	0.338	3.06	0.72	0.022	0.156	1.21
18	227	0.78	0.377	3.14	0.96	0.028	0.203	1.42
19	261	0.76	0.356	3.12	0.83	0.032	0.208	1.16
20	294	0.67	0.312	3.26	0.83	0.024	0.242	1.21

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
21	238	0.79	0.348	4.49	1.96	0.031	0.259	1.26
22	209	0.94	0.328	3.45	0.99	0.026	0.211	1.38
23	226	0.80	0.346	4.51	1.27	0.036	0.202	1.60
24	199	0.95	0.413	4.09	1.21	0.035	0.229	1.41
25	238	0.80	0.342	4.40	1.41	0.032	0.218	1.35

ORGAN WEIGHTS (GRAM)
AFTER 4 WEEKS
FEMALES

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
31	186	1.86	0.687	5.65	1.49	0.071	0.573	0.146
32	187	1.73	0.709	6.12	1.43	0.063	0.414	0.169
33	190	1.87	0.790	5.85	1.39	0.092	0.543	0.160
34	161	1.70	0.643	5.26	1.27	0.075	0.451	0.160
35	167	1.79	0.638	5.01	1.24	0.056	0.501	0.131

GROUP 2 (5 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
41	150	1.77	0.581	4.60	1.21	0.062	0.405	0.110
42	160	1.78	0.556	5.03	1.32	0.067	0.415	0.165
43	163	1.73	0.559	5.48	1.20	0.074	0.493	0.103
44	160	1.65	0.646	5.80	1.30	0.066	0.506	0.148
45	168	1.74	0.624	5.40	1.25	0.077	0.488	0.124

GROUP 3 (50 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
46	173	1.73	0.777	5.66	1.33	0.074	0.414	0.154
47	154	1.73	0.680	5.20	1.36	0.080	0.406	0.124
48	144	1.76	0.670	4.72	1.22	0.061	0.358	0.121
49	179	1.75	0.749	5.47	1.28	0.072	0.532	0.137
50	176	1.75	0.630	5.78	1.24	0.061	0.457	0.134

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
51	152	1.64	0.644	6.12	1.36	0.075	0.413	0.120
52	177	1.87	0.734	7.33	1.64	0.074	0.429	0.149
53	163	1.81	0.736	5.78	1.40	0.070	0.387	0.137
54	156	1.78	0.639	5.86	1.45	0.082	0.327	0.155
55	164	1.78	0.668	7.48	1.53	0.073	0.375	0.178

**ORGAN/BODY WEIGHT RATIOS (%)
AFTER 4 WEEKS
FEMALES**

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
31	186	1.00	0.369	3.04	0.80	0.038	0.308	0.078
32	187	0.93	0.379	3.27	0.77	0.034	0.221	0.090
33	190	0.98	0.416	3.08	0.73	0.048	0.286	0.084
34	161	1.06	0.399	3.27	0.79	0.047	0.280	0.099
35	167	1.07	0.382	3.00	0.74	0.034	0.300	0.078

GROUP 2 (5 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
41	150	1.18	0.387	3.07	0.80	0.041	0.270	0.073
42	160	1.11	0.348	3.15	0.83	0.042	0.259	0.103
43	165	1.05	0.339	3.32	0.73	0.045	0.299	0.062
44	160	1.03	0.404	3.63	0.81	0.041	0.316	0.093
45	168	1.03	0.371	3.21	0.74	0.046	0.290	0.074

GROUP 3 (50 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
46	173	1.00	0.449	3.27	0.77	0.043	0.239	0.089
47	154	1.12	0.442	3.37	0.88	0.052	0.264	0.081
48	144	1.22	0.465	3.28	0.85	0.042	0.249	0.084
49	179	0.98	0.418	3.06	0.72	0.040	0.297	0.077
50	176	1.00	0.358	3.28	0.71	0.035	0.260	0.076

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
51	152	1.08	0.424	4.02	0.90	0.049	0.272	0.079
52	177	1.06	0.415	4.14	0.92	0.042	0.242	0.084
53	163	1.11	0.452	3.55	0.86	0.043	0.237	0.084
54	156	1.14	0.410	3.76	0.93	0.053	0.210	0.099
55	164	1.08	0.407	4.56	0.93	0.045	0.229	0.109

ORGAN WEIGHTS (GRAM)
AFTER 8 WEEKS
MALES

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
6	307	1.98	0.888	7.71	1.72	0.062	0.475	3.32
7	322	2.05	0.889	9.01	1.73	0.071	0.657	2.95
8	346	1.95	1.181	9.11	2.01	0.066	0.510	3.20
9	307	1.85	1.012	7.10	1.64	0.070	0.370	3.23
10	315	1.96	1.098	7.78	1.81	0.077	0.538	3.60

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
26	261	1.85	0.680	6.19	1.61	0.055	0.540	3.70
27	280	1.95	0.792	6.99	1.83	0.066	0.498	3.00
28	307	1.91	0.995	7.46	2.06	0.076	0.645	3.53
29	278	1.81	0.957	7.09	2.24	0.048	0.465	3.19
30	272	1.84	0.771	7.42	2.06	0.067	0.517	3.74

NOTOX Project 126282
TKK 30059 (ZK RT 1507)

OW-IND - 6
06-DEC-94

ORGAN/BODY WEIGHT RATIOS (%)
AFTER 8 WEEKS
MALES

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
6	307	0.64	0.289	2.51	0.56	0.020	0.155	1.08
7	322	0.64	0.276	2.80	0.54	0.022	0.204	0.92
8	346	0.56	0.341	2.63	0.58	0.019	0.147	0.92
9	307	0.60	0.330	2.31	0.53	0.023	0.121	1.05
10	315	0.62	0.349	2.47	0.58	0.024	0.171	1.14

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	TESTES
26	261	0.71	0.261	2.37	0.62	0.021	0.207	1.42
27	280	0.70	0.283	2.50	0.65	0.024	0.178	1.07
28	307	0.62	0.324	2.43	0.67	0.025	0.210	1.15
29	278	0.65	0.344	2.55	0.80	0.017	0.167	1.15
30	272	0.67	0.283	2.73	0.76	0.025	0.190	1.37

ORGAN WEIGHTS (GRAM)
AFTER 8 WEEKS
FEMALES

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
36	192	1.81	0.726	5.08	1.36	0.074	0.353	0.141
37	193	1.87	0.706	6.23	1.58	0.080	0.403	0.164
38	188	1.70	0.695	5.87	1.23	0.067	0.412	0.136
39	192	1.70	0.637	4.91	1.30	0.071	0.363	0.150
40	207	1.75	0.782	5.53	1.30	0.072	0.460	0.184

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W.	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
56	208	1.90	0.788	6.96	1.66	0.072	0.618	0.169
57	175	1.90	0.715	4.83	1.30	0.062	0.366	0.150
58	196	1.79	0.673	5.97	1.89	0.111	0.622	0.191
59	210	1.73	0.794	6.85	1.51	0.094	0.465	0.182
60	179	1.75	0.640	5.30	1.22	0.064	0.413	0.123

ORGAN/BODY WEIGHT RATIOS (%)
AFTER 8 WEEKS
FEMALES

GROUP 1 (CONTROL)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
36	192	0.94	0.378	2.65	0.71	0.039	0.184	0.073
37	193	0.97	0.366	3.23	0.82	0.041	0.209	0.085
38	188	0.90	0.370	3.12	0.65	0.036	0.219	0.072
39	192	0.88	0.332	2.56	0.68	0.037	0.189	0.078
40	207	0.84	0.378	2.67	0.63	0.035	0.222	0.089

GROUP 4 (250 MG/KG)

ANIMAL NUMBER	BODY W. (GRAM)	BRAIN	HEART	LIVER	KIDNEYS	ADRENALS	SPLEEN	OVARIES
56	208	0.91	0.379	3.35	0.80	0.035	0.297	0.081
57	175	1.08	0.409	2.76	0.74	0.035	0.209	0.086
58	196	0.91	0.343	3.05	0.96	0.057	0.317	0.097
59	210	0.82	0.378	3.26	0.72	0.045	0.221	0.087
60	179	0.98	0.358	2.96	0.68	0.036	0.231	0.069



APPENDIX 1
ANALYTICAL REPORT

FOR

NOTOX Project 126282

NOTOX Substance TKK 30059 (ZK RT 1507)
NOTOX Substance No. 43092

REPORT APPROVAL

PRINCIPAL SCIENTIST:

Dr. Ir. M.M. Gladdines


date: 23 December 1994

PREFACE

**Study plan
(analytical study)**

Start: 29 July 1994
Completed: 04 August 1994

PURPOSE

The purpose of the study was to determine the concentrations, stability and homogeneity of TKK 30059 (ZK RT 1507) in Corn oil.

NOMINAL CONCENTRATIONS

GROUP 1	0 mg/ml =	0 mg/g
GROUP 2	1 mg/ml =	1.09 mg/g
GROUP 3	10 mg/ml =	10.9 mg/g
GROUP 4	50 mg/ml =	54.1 mg/g

REAGENTS

Milli-Q water	Tap water purified by reversed osmosis and subsequently passed over activated carbon and ion-exchange cartridges: Millipore Corp., Bedford, MA, USA
Acetonitrile	HPLC, Labscan, Dublin, Ireland
Phosphoric acid	85%, pro analysi, Merck, Darmstadt, Germany

SAMPLE HANDLING**Determination of the concentrations**

All formulations prepared on 29 July 1994, 02 and 04 August 1994 were analysed for test substance concentration.

Determination of the stability testing

The formulations of groups 2 and 4 prepared on 29 July 1994, 02 and 04 August 1994 were analysed immediately after preparation and after 4 hours storage at ambient temperature.

Determination of the homogeneity

The formulations of groups 2 and 4 prepared on 29 July 1994, 02 and 04 August 1994 were tested for homogeneity.

SAMPLING PROCEDURE

Samples for the determination of the concentrations and stability were taken at 50% height from the formulation. For the determination of the homogeneity three samples were taken: one at the top (at 90% height), one at the middle (at 50% height) and one at the bottom (at 10% height).

SAMPLE PRETREATMENT

All samples were weighed accurately using an analytical balance in a volumetric flask. The flask was filled to up the mark using acetonitrile. The samples of group 3 and 4 were further diluted using acetonitrile to obtain suitable concentrations for analysis.

All practical handlings (e.g. dilution, filling up the HPLC vials) were performed under red light conditions.

QUANTITATIVE ANALYSIS

Calibration curve

Starting from two independently prepared stock solutions of TKK 30059 (ZK RT 1507) in acetonitrile, six dilutions in mobile phase were prepared in the concentration range of 7.8 to 28 mg/l. The response was correlated with the concentration test substance, using linear regression analysis (least squares method).

DATA HANDLING

Response: $R = \text{Peak area test substance [units]}$

Calibration curve:

$$R = a * C + b$$

R = response calibration solution [units]
 C = concentration of test substance in calibration solution [mg/l]
 a = slope [units*1/mg]
 b = intercept [units]

Concentration analysed:

$$C = \frac{(R-b) * V * d}{a * w} [\text{mg/g}]$$

R = response sample [units]
 V = volume volumetric flask [ml]
 d = dilution factor [units*1/mg]
 a = slope [units*1/mg]
 b = intercept [units]
 w = weight sample [mg]

Relative concentration:

$$\frac{\text{Concentration analysed}}{\text{Concentration prepared}} * 100 [\%]$$

Relative to mean concentration:

$$\frac{\text{Concentration analysed}}{\text{Mean of concentrations analysed of 6 samples}} * 100 [\%]$$

Relative Difference (Rel. Diff.):

$$\frac{\text{Mean Conc. analysed } t=4 - \text{Mean Conc. analysed } t=0}{\text{Mean Concentration analysed } t=0} * 100\%$$

t = time of sampling [hours]

HPLC CONDITIONS

Analysis

Column	LiChrospher 60 RP-select B, 250 x 4 (I.D.) mm; $d_p=5 \mu\text{m}$ (Merck, Darmstadt, Germany)
Mobile phase	60/40/0.1 (v/v/v) Acetonitrile / Milli-Q water / Phosphoric acid
Flow	1 ml/min
Detection	UV at $\lambda= 222 \text{ nm}$
Injection volume	10 μl

RESULTS

The results are summarised in Tables 1-6.
 Analysis of the pretreatment samples, measured on 29 July 1994, revealed unacceptable results due to inhomogeneity of the formulations.
 Therefore, for further analysis, the formulations were shaken vigorously before sampling.

TABLE 1 Concentrations of TKK 30059 (ZK RT 1507) in vehicle (pretreatment).

Group	Date of analysis	Concentration [mg/g]		
		Prepared	Analysed ¹	Relative [%]
1	02-08-1994	0	-/-	-/-
2	02-08-1994	1.09	1.19 / 1.05	109/96
3	02-08-1994	10.9	10.7 / 10.8	98/99
4	02-08-1994	54.1	49.2 / 50.9	91/94

¹ Results of duplicate samples.

TABLE 2 Homogeneity of TKK 30059 (ZK RT 1507) in vehicle (pretreatment).

Group	Date of analysis	Sampling position [height]	Concentration [mg/g]		
			Prepared	Analysed ¹	Relative to mean
2	02-08-1994	90%	1.09	1.12/1.15	99/102
		50%		1.19/1.05	105/ 93
		10%		1.17/1.11	103/ 98
4	02-08-1994	90%	54.1	52.1/52.0	101/101
		50%		49.2/50.9	95/ 98
		10%		52.4/53.5	101/104

¹ Results of duplicate samples.

TABLE 3 Stability of TKK 30059 (ZK RT 1507) in vehicle (pretreatment).

Group	Date of analysis	Concentration analysed ¹ [mg/g]		
		t=0 [hours]	t=4 [hours]	Rel. Diff. [%]
2	02-08-1994	1.19/1.05	1.14/1.20	+4.5
4	02-08-1994	49.2/50.9	49.4/47.4	-3.3

¹ Results of duplicate samples.

TABLE 4 Concentrations of TKK 30059 (ZK RT 1507) in vehicle (main study).

Group	Date of analysis	Concentration [mg/g]		
		Prepared	Analysed ¹	Relative [%]
1	04-08-1994	0	-/-	-/-
2	04-08-1994	1.08	0.99 / 1.03	92/95
3	04-08-1994	10.9	10.2 / 11.2	94/103
4	04-08-1994	54.1	53.4 / 50.8	99/94

¹ Results of duplicate samples.

TABLE 5 Homogeneity of TKK 30059 (ZK RT 1507) in vehicle (main study).

Group	Date of analysis	Sampling position [height]	Concentration [mg/g]		
			Prepared	Analysed ¹	Relative to mean
2	04-08-1994	90%	1.08	1.15/0.97	115 / 97
		50%		0.99/1.03	99/103
		10%		0.98/0.88	98 / 88
4	04-08-1994	90%	54.1	51.4/50.0	102/100
		50%		53.4/50.8	106/101
		10%		48.0/47.6	96 / 95

¹ Results of duplicate samples.

TABLE 6 Stability of TKK 30059 (ZK RT 1507) in vehicle (main study).

Group	Date of analysis	Concentration analysed ¹ [mg/g]		
		t=0 [hours]	t=4 [hours]	Rel. Diff. [%]
2	04-08-1994	0.99/1.03	0.86/0.79	-18.3
4	04-08-1994	53.4/50.8	58.2/56.0	+9.6

¹ Results of duplicate samples.

APPENDIX 2
PATHOLOGY REPORT

FOR

NOTOX Project 126282

NOTOX Substance TKK 30059 (ZK RT 1507)
NOTOX Substance No. 43092

PATHOLOGY REPORT

PAGE : I
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF CONTENTS

	PAGE :
AUTHENTICATION	3
PRINCIPAL SECTION SUMMARY	4
METHODS	5 - 6
RESULTS	7
CONCLUSIONS	8
EXPLANATION OF CODES AND SYMBOLS	9
SUMMARY TABLES	
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K1	10 - 11
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: R1	12 - 13
INDIVIDUAL ANIMAL DATA	
TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS	14 - 19
ANIMAL HEADING DATA DOSE GROUP 01	20
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 01	21 - 30
ANIMAL HEADING DATA DOSE GROUP 02	31
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 02	32 - 37
ANIMAL HEADING DATA DOSE GROUP 03	38
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 03	39 - 44
ANIMAL HEADING DATA DOSE GROUP 04	45
TEXT OF GROSS AND MICROSCOPIC FINDINGS DOSE GROUP 04	46 - 62

PATHOLOGY REPORT

PAGE : 3
TOX NO.: 126282

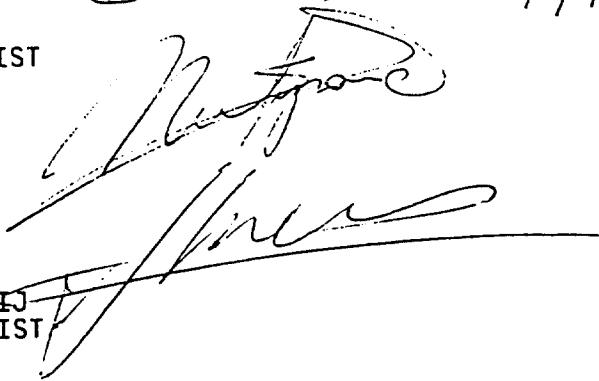
TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

AUTHENTICATION

The undersigned hereby declares that the histopathology data in this report were compiled by her/him, and that they reflect accurately the primary data records.

Date:

December, 27 1994

DRS. MARCEL WIJNANDS
TOXICOLOGICAL PATHOLOGIST

DATA CROSS-CHECKED BY:

DR. JOOP VAN NESSELROOIJ
TOXICOLOGICAL PATHOLOGIST

NOTOX B.V.
HAMBAKENWETERING 3
5231 DD
'S-HERTOGENBOSCH

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 4
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

SUMMARY

Groups of 5 male and 5 female rats were dosed orally by gavage with 5, 50 or 250 mg/kg body weight/day of TKK 30059 (ZK RT 1507) for 28 days. A further control group received Corn oil only. The control and 250 mg/kg groups contained 5 additional animals per sex, which were allowed a further 4 weeks recovery. After 4 weeks (test period) and 8 weeks (test and recovery period) the animals were killed and detailed necropsy examination performed. Sections of protocol listed tissues were examined from the control and the high dose groups, and from macroscopically changed tissues from all groups. In addition, all stomachs and kidneys of the low and mid-dose groups were examined.

Microscopic examination revealed degenerative tubular changes in the kidneys of all treated males and of high dose females. The kidneys of the high dose recovery animals showed a regenerative process. A submucosal inflammatory reaction in the stomach was seen in nearly all mid and high dose animals. This phenomenon was still seen in a few male and female animals of the high dose recovery group.

Oral administration of TKK 30059 (ZK RT 1507) for 28 days at the lowest dose level of 5 mg/kg body weight per day still produced histopathological evidence of toxicity.

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 5
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

METHODS

At termination of the experiment, rats were fasted overnight and then killed by exsanguination under deep ether anaesthesia. At necropsy, all animals were subjected to detailed post-mortem examination.

All macroscopic abnormalities observed at necropsy were recorded.

The weights of the adrenals, brain, heart, kidneys, liver, ovaries, spleen and testes were recorded.

The following tissues were removed and fixed, whole or in part, in 4% buffered neutral formaldehyde solution.

Adrenals, aorta, brain, cecum, cervix, clitoral glands, colon, duodenum, epididymides, esophagus, eyes with optical nerve and Harderian glands, female mammary gland area, femur including joint, heart, ileum, jejunum, kidneys, larynx, exorbital lacrimal glands, liver, lungs, lymph nodes (mandibular and mesenteric) nasopharynx, ovaries, pancreas, pituitary gland, preputial glands, prostatic gland, rectum, salivary glands (mandibular and sublingual), sciatic nerve, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, sternum with bone marrow, stomach, testes, thymus, thyroid including parathyroids, tongue, trachea, urinary bladder, uterus, vagina and all gross lesions.

The tissues listed below were trimmed, processed and embedded in paraffin wax and sectioned at a thickness of 2-4 micrometres.

Adrenals, heart, kidneys, liver, spleen, stomach and testes from all control and high dose animals.

Stomach and kidneys of the low- and mid-dose groups. Any gross lesions.

Sections were stained with haematoxylin and eosin.

Stained sections were examined light microscopically and the findings were entered into the pathology computer system under experiment 94025.

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 6
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

METHODS

Data compilation

The animal data and macroscopic findings were transferred from the toxicological data management system by an intersystem transfer into the PATHDATA system.

The microscopic findings were recorded by the undersigned pathologist using on-line input into the PATHDATA computer system.

All macroscopic and microscopic findings are given for each animal in text form under "Text of Gross and Microscopic Findings". The incidence of microscopic findings is also presented in tabular form. Incidence tables are created by computer.

Histologic changes were described, whenever possible, according to distribution, severity and morphologic character. Severity scores were assigned as given under "Explanation of Codes and Symbols".

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 7
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

RESULTS

Macroscopic findings

Male and female animals of the high and mid dose groups showed macroscopic changes of the stomach such as glandular mucosa wall thickening and only the male animals of these dose groups showed enlargement and pale discoloration of the kidneys. After 4 weeks of recovery, one female animal of the high dose group showed a thickening of the limiting ridge of the stomach and an irregular surface of the kidneys. An overgrowth of the upper incisors was seen in both male and female animals of the high dose recovery groups.

Microscopic findings

In the stomach of most of the mid and high dose group animals gastritis was seen. This was characterized by submucosal edema, hyperemia and polymorphonuclear cell infiltrate. These changes were mainly seen just beyond the limiting ridge. Immediately after the limiting ridge, erosion, a damage of the mucosal surface was noted. Gastritis was still detectable in a few animals of the recovery group.

All male animals of all dose groups and all females of the high dose group showed degenerative kidney changes. The kidneys of the high dose recovery males showed some regeneration (basophilic tubules) and scar tissue (fibrosis). The kidneys of the female low and mid dose groups were not affected. One of the high dose recovery females showed moderate inflammation. At the end of the recovery period it was apparent that the incidence of mineral deposition in the kidney of high dose females was reduced.

The small number of other findings recorded are within the normal range of background alterations which may be seen in untreated rats of this age and strain.

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 8
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507)
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL.
SPONSOR : Ciba-Geigy AG

PATHOL. NO.: 94025 WIM
DATE : 23-DEC-94
PATHDATA SYSTEM V3.5d

CONCLUSIONS

After administration of the test substance for 28-days a variety of histopathological changes in the kidneys were noted in all treated males and in the high dose females and in the stomach of nearly all mid and high dose animals. The induced changes had an overall degenerative or inflammatory character.

The high dose recovery groups showed some regeneration of the kidneys while gastritis was still seen in the stomach of a few animals.

The overgrowth of the upper incisors was possibly caused by a mineral loss due to a nephrotoxic effect of the test substance.

The oral administration of TKK 30059 (ZK RT 1507) to rats for 28 days at the lowest level of 5 mg/kg/day still produced pathological evidence of toxicity.

END OF REPORT SECTION

PATHOLOGY REPORT

PAGE : 9
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL

M = MALE ANIMAL
F = FEMALE ANIMAL
K1 = INTERIM SACRIFICE
R1 = RECOVERY / POST-TREATMENT GROUPS

CODES AND SYMBOLS USED AT ORGAN LEVEL:

G = GROSS OBSERVATION CHECKED OFF HISTOLOGICALLY
,

= HISTOLOGIC EXAMINATION NOT REQUIRED
+ = ORGAN EXAMINED, FINDINGS PRESENT
- = ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1 = MINIMAL / VERY FEW / VERY SMALL
GRADE 2 = SLIGHT / FEW / SMALL
GRADE 3 = MODERATE / MODERATE NUMBER / MODERATE SIZE
GRADE 4 = MARKED / MANY / LARGE
(= FINDING UNILATERAL IN PAIRED ORGANS

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 10
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K1

ORGAN/FINDING	SEX DOSE GROUP: NO. ANIMALS:	MALE			
		01	02	03	04
HEART	NO. EXAM.:	5		5	
LIVER	NO. EXAM.:	5		5	
- RES AGGREGATES		2			
SPLEEN	NO. EXAM.:	5		5	
KIDNEYS	NO. EXAM.:	5	5	5	5
- TUBULAR DILATION			3	5	
- TUBULAR DEGENERATION		5	5	5	
- HYDRONEPHROSIS		1	1		
- PROTEINACEOUS CASTS			4	5	
- HYAL. RESORPT. BODIES		5	5	5	
- POLYMORPHONUCL/INF.				1	
- MONONUCLEAR/INF		1	1	4	
- UROTHEL. HYPERPLASIA			2		
- BASOPHILIC TUBULES					
STOMACH	NO. EXAM.:	5	5	5	5
- GASTRITIS/GLANDULAR		1	4	4	
- EROSION/GLANDULAR			1	5	
- HYPERKERATOSIS				3	
TESTES	NO. EXAM.:	5		5	
ADRENAL GLANDS	NO. EXAM.:	5		5	

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 11
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K1

ORGAN/FINDING	SEX DOSE GROUP: NO. ANIMALS:					FEMALE
		01	02	03	04	
HEART	NO. EXAM.:	5			5	
LIVER	NO. EXAM.:	5			5	
- RES AGGREGATES		1				
- LYMPHOID CELL INFIL.				1		
SPLEEN	NO. EXAM.:	5			5	
KIDNEYS	NO. EXAM.:	5	5	5	5	
- TUBULAR DILATION					5	
- TUBULAR DEGENERATION					3	
- HYDRONEPHROSIS		1				
- PROTEINACEOUS CASTS					4	
- UROTHEL HYPERPLASIA					1	
- MINERAL/CORTICOMED.		5	5	4	5	
- BASOPHILIC TUBULES		1	2			
STOMACH	NO. EXAM.:	5	5	5	5	
- GASTRITIS/GLANDULAR		1		4	4	
- EROSION/GLANDULAR					4	
- HYPERKERATOSIS				3	5	
ADRENAL GLANDS	NO. EXAM.:	5			5	

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 12
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1

ORGAN/FINDING	SEX DOSE GROUP: NO. ANIMALS:	MALE			
		01	02	03	04
HEART	NO. EXAM.:	5		5	
LIVER	NO. EXAM.:	5		5	
- RES AGGREGATES				3	
SPLEEN	NO. EXAM.:	5		5	
KIDNEYS	NO. EXAM.:	5		5	
- TUBULAR DILATION				2	
- PROTEINACEOUS CASTS				1	
- MONONUCLEAR/INF				3	
- MINERAL/CORTICOMED.				1	
- BASOPHILIC TUBULES				4	
- FIBROSIS/CORTICAL				2	
- CYST(S)				1	
STOMACH	NO. EXAM.:	5		5	
- GASTRITIS/GLANDULAR				2	
- HYPERKERATOSIS				1	
TESTES	NO. EXAM.:	5		5	
ADRENAL GLANDS	NO. EXAM.:	5		5	

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 13
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1

ORGAN/FINDING	SEX DOSE GROUP: NO. ANIMALS:	FEMALE			
		01	02	03	04
HEART	NO. EXAM.:	5		5	
LIVER	NO. EXAM.:	5		5	
- RES AGGREGATES				1	
- CONSTRICTION			1		
- FOCAL FIBROSIS			1		
SPLEEN	NO. EXAM.:	5		5	
KIDNEYS	NO. EXAM.:	5		5	
- MINERAL/CORTICOMED.		5		2	
- CHRON INT NEPHRITIS				1	
STOMACH	NO. EXAM.:	5		5	
- GASTRITIS/GLANDULAR				3	
ADRENAL GLANDS	NO. EXAM.:	5		5	
SKIN	NO. EXAM.:	1			
OVARIES	NO. EXAM.:			1	

END OF REPORT SECTION

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 14
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO. : 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 15
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER :

31 32 33 34 35 36 37 38 39 40
FK1 FK1 FK1 FK1 FK1 FR1 FR1 FR1 FR1 FR1

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 16
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 02, 5 MG/KG

ANIMAL NUMBER :

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 17
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 03. 50 MG/KG

ANIMAL NUMBER :

16 17 18 19 20 46 47 48 49 50
MK1 MK1 MK1 MK1 MK1 FK1 FK1 FK1 FK1 FK1

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 18
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

ANIMAL NUMBER :

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 19
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

ANIMAL NUMBER :

	51 FK1	52 FK1	53 FK1	54 FK1	55 FK1	56 FR1	57 FR1	58 FR1	59 FR1	60 FR1
--	-----------	-----------	-----------	-----------	-----------	-----------	-----------	-----------	-----------	-----------

HEART	-	-	-	-	-	-	-	-	-	-
LIVER	-	-	+	-	-	-	-	+	-	-
- RES AGGREGATES	1.	.	.	.
- LYMPHOID CELL INFIL.	.	.	1.
SPLEEN	-	-	-	-	-	-	-	-	-	-
KIDNEYS	+	+	+	+	+	-	+	+G	-	+
- TUBULAR DILATION	1.	1.	1.	1.	1.
- TUBULAR DEGENERATION	1.	1.	1.
- PROTEINACEOUS CASTS	1.	1.	1.	.	1.
- UROTHEL.HYPERPLASIA	1.
- MINERAL/CORTICOMED.	1.	1.	1.	1.	1.	.	1.	.	.	1.
- CHRON INT NEPHRITIS	3.	.	.
STOMACH	+G	+G	+G	+G	+G	+	-	+G	-	+
- GASTRITIS/GLANDULAR	1.	3.	1.	.	2.	2.	.	2.	.	1.
- EROSION/GLANDULAR	2.	2.	.	2.	3.
- HYPERKERATOSIS	2.	1.	1.	1.	2.
ADRENAL GLANDS	-	-	-	-	-	-	-	-	-	-
ORAL CAVITY	;	;	;	;	;	;	G	G	G	;
SKIN	;	;	;	;	;	;	;	;	;	;
OVARIES	;	;	;	;	;	;	;	-G	;	;
GENERAL OBSERVATIONS	;	;	;	;	;	;	;	;	;	;

END OF REPORT SECTION

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 20
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

ANIMAL HEADING DATA
DOSE GROUP : 01, CONTROL

ANIMAL NUMBER	SEX M/F	DEFINED AND FINAL STATE OF NECROPSY	TEST DAYS	FIRST AND LAST DAY UNDER TEST	DATE OF NECROPSY
1	M	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
2	M	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
3	M	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
4	M	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
5	M	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
6	M	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
7	M	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
8	M	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
9	M	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
10	M	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
.....
31	F	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
32	F	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
33	F	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
34	F	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
35	F	K1	K1	28 03-AUG-94	30-AUG-94 31-AUG-94
36	F	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
37	F	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
38	F	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
39	F	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
40	F	R1	R1	28 03-AUG-94	30-AUG-94 28-SEP-94
.....

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE 21
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS MALE
DOSE GROUP : 01, CONTROL

* STATE AT NECROPSY: K1 * ANIMAL NO. : 1
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 2
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 3
DAYS ON TEST : 28

* NECROPSY FINDINGS

KIDNEYS:

RIGHT SIDE: PELVIC DILATION.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 22
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO. : 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

CONT./FF. ANIMAL NO. : 3

* MICROSCOPIC FINDINGS

LIVER:

-AGGREGATES OF RES CELLS, GRADE 1

KIDNEYS:

-HYDRONEPHROSIS, UNILATERAL, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1

DAYS ON TEST : 28

* ANIMAL NO. : 4

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-AGGREGATES OF RES CELLS, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1

DAYS ON TEST : 28

* ANIMAL NO. : 5

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 23
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

CONT./FF. ANIMAL NO. : 5

.....
* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

.....
* STATE AT NECROPSY: R1
DAYS ON TEST : 28

* ANIMAL NO. : 6

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

.....
* STATE AT NECROPSY: R1
DAYS ON TEST : 28

* ANIMAL NO. : 7

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 24
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO. : 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 8
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: R1 * ANIMAL NO. : 9
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: R1 * ANIMAL NO. : 10
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 25
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

MALE

CONT./FF. ANIMAL NO. : 10

.....
* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 26
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO. : 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 31
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 32
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-AGGREGATES OF RES CELLS, GRADE 1

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 2

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 27
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS FEMALE
DOSE GROUP : 01, CONTROL

* STATE AT NECROPSY: K1 * ANIMAL NO. : 33
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

- CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 2
- BASOPHILIC TUBULES, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 34
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

- CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 28
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

* STATE AT NECROPSY: K1
DAYS ON TEST : 28 * ANIMAL NO. : 35

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-HYDRONEPHROSIS, UNILATERAL, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1
DAYS ON TEST : 28 * ANIMAL NO. : 36

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 29
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507)
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL.
SPONSOR : Ciba-Geigy AG

PATOL. NO.: 94025 WIM
DATE : 23-DEC-94
PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL

FEMALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 28

* ANIMAL NO. : 37

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1
DAYS ON TEST : 28

* ANIMAL NO. : 38

* NECROPSY FINDINGS

LIVER:

LEFT MEDIAN LOBE: DIAPHRAGMATIC HERNIA.

SKIN:

CHEEK REGION, LEFT SIDE: ALOPECIA.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:

-CONSTRICKTION, GRADE 2
-FOCAL FIBROSIS, GRADE 2

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

SKIN:

NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 30
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, CONTROL FEMALE

* STATE AT NECROPSY: R1
DAYS ON TEST : 28 * ANIMAL NO. : 39

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1
DAYS ON TEST : 28 * ANIMAL NO. : 40

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 31
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

ANIMAL HEADING DATA
DOSE GROUP : 02, 5 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY	
11	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
12	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
13	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
14	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
15	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
41	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
42	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
43	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
44	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
45	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 32
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 5 MG/KG

MALE

* STATE AT NECROPSY: K1
DAYS ON TEST : 28

* ANIMAL NO. : 11

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: K1
DAYS ON TEST : 28

* ANIMAL NO. : 12

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 33
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS MALE
DOSE GROUP : 02, 5 MG/KG

* STATE AT NECROPSY: K1 * ANIMAL NO. : 13
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 1

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1

* STATE AT NECROPSY: K1 * ANIMAL NO. : 14
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 34
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 5 MG/KG

MALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 15
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 1
- UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 35
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS FEMALE
DOSE GROUP : 02, 5 MG/KG

* STATE AT NECROPSY: K1 * ANIMAL NO. : 41
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
-BASOPHILIC TUBULES, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: K1 * ANIMAL NO. : 42
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 36
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 5 MG/KG

FEMALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 43
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

* STATE AT NECROPSY: K1 * ANIMAL NO. : 44
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 37
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS FEMALE
DOSE GROUP : 02, 5 MG/KG

* STATE AT NECROPSY: K1 * ANIMAL NO. : 45
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
-BASOPHILIC TUBULES, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 38
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

ANIMAL HEADING DATA

DOSE GROUP : 03. 50 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY	
16	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
17	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
18	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
19	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
20	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
46	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
47	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
48	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
49	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
50	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 39
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507)
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL.
SPONSOR : Ciba-Geigy AG

PATHOL. NO.: 94025 WIM
DATE : 23-DEC-94
PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 50 MG/KG

MALE

* STATE AT NECROPSY: K1
DAYS ON TEST : 28 * ANIMAL NO. : 16

.....
* NECROPSY FINDINGS

KIDNEYS:
DISCOLOURATION, PALE.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 2
-BASOPHILIC TUBULES, GRADE 1

STOMACH:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

.....
* STATE AT NECROPSY: K1
DAYS ON TEST : 28 * ANIMAL NO. : 17

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 1
-BASOPHILIC TUBULES, GRADE 1

STOMACH:
-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 40
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO. : 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 50 MG/KG

MALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 18
DAYS ON TEST : 28

* NECROPSY FINDINGS

KIDNEYS:

ENLARGED, DISCOLOURATION, PALE.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
 - TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
 - PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
 - HYALINE RESORPTION BODIES, TUBULAR, GRADE 2
- STOMACH:
- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2
 - EROSION GLANDULAR STOMACH, GRADE 1

* STATE AT NECROPSY: K1 * ANIMAL NO. : 19
DAYS ON TEST : 28

* NECROPSY FINDINGS

KIDNEYS:

ENLARGED, DISCOLOURATION, PALE.

STOMACH:

GLANDULAR MUCOSA, WALL: THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 41
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 50 MG/KG

MALE

CONT./FF. ANIMAL NO. : 19

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- HYDRONEPHROSIS, UNILATERAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 1
- MONONUCLEAR CELL INFILTRATE (MULTI)FOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1

* STATE AT NECROPSY: K1

DAYS ON TEST : 28

* ANIMAL NO. : 20

* NECROPSY FINDINGS

KIDNEYS:

DISCOLOURATION, PALE.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 1
- UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 42
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 50 MG/KG

FEMALE

* STATE AT NECROPSY: K1
DAYS ON TEST : 28

* ANIMAL NO. : 46

* NECROPSY FINDINGS

STOMACH:

GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 3
-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 3

* STATE AT NECROPSY: K1

DAYS ON TEST : 28

* ANIMAL NO. : 47

* NECROPSY FINDINGS

STOMACH:

GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2

-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 43
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 50 MG/KG FEMALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 48
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
STOMACH:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING

* STATE AT NECROPSY: K1 * ANIMAL NO. : 49
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
STOMACH:
-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 44
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 50 MG/KG

FEMALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 50
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
STOMACH:
-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2
-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1

**PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA**

PAGE : 45
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

ANIMAL HEADING DATA
DOSE GROUP : 04, 250 MG/KG

ANIMAL NUMBER	SEX M/F	DEFINED STATE OF NECROPSY	TEST DAYS	FIRST DAY UNDER TEST	LAST DAY UNDER TEST	DATE OF NECROPSY	
21	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
22	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
23	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
24	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
25	M	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
26	M	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
27	M	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
28	M	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
29	M	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
30	M	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
51	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
52	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
53	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
54	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
55	F	K1	K1	28	03-AUG-94	30-AUG-94	31-AUG-94
56	F	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
57	F	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
58	F	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
59	F	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94
60	F	R1	R1	28	03-AUG-94	30-AUG-94	28-SEP-94

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 46
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

MALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 21
DAYS ON TEST : 28

* NECROPSY FINDINGS

KIDNEYS:
ENLARGED, DISCOLOURATION, PALE.

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 3
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 2
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 2
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 4
- POLYMORPHONUCLEAR CELL INFILTRATE, (MULTI)FOCAL, GRADE 2
- UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 2

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2
- EROSION GLANDULAR STOMACH, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 22
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 47
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG MALE

CONT./FF. ANIMAL NO. : 22

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 3

STOMACH:

- NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING
- EROSION GLANDULAR STOMACH, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1

DAYS ON TEST : 28

* ANIMAL NO. : 23

* NECROPSY FINDINGS

KIDNEYS:

- ENLARGED, DISCOLOURATION, PALE.

STOMACH:

- GLANDULAR MUCOSA, WALL: THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 2
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 4
- UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1
- EROSION GLANDULAR STOMACH, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 48
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

MALE

CONT./FF. ANIMAL NO. : 23

-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 24
DAYS ON TEST : 28

* NECROPSY FINDINGS

KIDNEYS:
ENLARGED, DISCOLOURATION, PALE.
STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR DILATION, MULTIFOCAL, GRADE 2
-TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
-PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
-HYALINE RESORPTION BODIES, TUBULAR, GRADE 3
-UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 3
STOMACH:
-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2
-EROSION GLANDULAR STOMACH, GRADE 2
-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 3
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 49
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG MALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 25
DAYS ON TEST : 28

* NECROPSY FINDINGS

KIDNEYS:

ENLARGED, DISCOLOURATION, PALE.

STOMACH:

GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 2
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 2
- HYALINE RESORPTION BODIES, TUBULAR, GRADE 3
- UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1
- EROSION GLANDULAR STOMACH, GRADE 2
- HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1 * ANIMAL NO. : 26
DAYS ON TEST : 28

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE, LEFT UPPER INCISOR MISSING.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 50
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG MALE

CONT./FF. ANIMAL NO. : 26

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

-AGGREGATES OF RES CELLS, GRADE 1

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-BASOPHILIC TUBULES, GRADE 1

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1

TESTES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 27
DAYS ON TEST : 28

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 51
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

MALE

CONT./FF. ANIMAL NO. : 27

SPLEEN:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
KIDNEYS:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
STOMACH:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
TESTES:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
ADRENAL GLANDS:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
ORAL CAVITY:
ORGAN NOT EXAMINED
MICROSCOPY NOT APPLICABLE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 28
DAYS ON TEST : 28

* NECROPSY FINDINGS

ORAL CAVITY:
JAW(S): INCISORS WHITE, UPPER INCISORS MISSING.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
LIVER:
-AGGREGATES OF RES CELLS, GRADE 1
SPLEEN:
ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
KIDNEYS:
-TUBULAR DILATION, MULTIFOCAL, GRADE 1
-PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
-MONONUCLEAR CELL INFILTRATE (MULTI)FOCAL, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 52
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

MALE

CONT./FF. ANIMAL NO. : 28

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

-BASOPHILIC TUBULES, GRADE 1

STOMACH:

-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1

TESTES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED
ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 29
DAYS ON TEST : 28

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE AND OVERGROWTH.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

-AGGREGATES OF RES CELLS, GRADE 1

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-TUBULAR DILATION, MULTIFOCAL, GRADE 1

-MONONUCLEAR CELL INFILTRATE (MULTI)FOCAL, GRADE 1

-BASOPHILIC TUBULES, GRADE 2

-CORTICAL INTERSTITIAL FIBROSIS, MULTIFOCAL, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 53
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG MALE

CONT./FF. ANIMAL NO. : 29

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2

TESTES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

* STATE AT NECROPSY: R1
DAYS ON TEST : 28

* ANIMAL NO. : 30

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-MONONUCLEAR CELL INFILTRATE (MULTI)FOCAL, GRADE 1

-BASOPHILIC TUBULES, GRADE 2

-CORTICAL INTERSTITIAL FIBROSIS, MULTIFOCAL, GRADE 1

-CYST(S), GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 54
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

MALE

CONT./FF. ANIMAL NO. : 30

TESTES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 55
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG FEMALE

* STATE AT NECROPSY: K1 * ANIMAL NO. : 51
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:

GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
- CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1
- EROSION GLANDULAR STOMACH, GRADE 2
- HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 52
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:

GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 56
TOX NO. : 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 52

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
- CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 3
- EROSION GLANDULAR STOMACH, GRADE 2
- HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1

DAYS ON TEST : 28

* ANIMAL NO. : 53

* NECROPSY FINDINGS

STOMACH:

LIMITING RIDGE: THICKENED.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

LIVER:

- LYMPHOID CELL INFILTRATION, FOCAL, GRADE 1

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- TUBULAR DEGENERATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL,
GRADE 1
- CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1
- HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 57
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 53

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 54
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

KIDNEYS:
-TUBULAR DILATION, MULTIFOCAL, GRADE 1
-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1
STOMACH:
-EROSION GLANDULAR STOMACH, GRADE 2
-HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K1 * ANIMAL NO. : 55
DAYS ON TEST : 28

* NECROPSY FINDINGS

STOMACH:
GLANDULAR MUCOSA, WALL: THICKENED; LIMITING RIDGE:
THICKENED.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 58
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 55

* MICROSCOPIC FINDINGS

KIDNEYS:

- TUBULAR DILATION, MULTIFOCAL, GRADE 1
- PROTEINACEOUS CASTS, INTRATUBULAR, CORTICAL, MULTIFOCAL, GRADE 1
- UROTHELIAL HYPERPLASIA, (MULTI)FOCAL, GRADE 1
- CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

- GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2
- EROSION GLANDULAR STOMACH, GRADE 3
- HYPERKERATOSIS, FORESTOMACH, DIFFUSE, GRADE 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: R1

DAYS ON TEST : 28

* ANIMAL NO. : 56

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 59
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG FEMALE

CONT./FF. ANIMAL NO. : 56

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 57
DAYS ON TEST : 28

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.
ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

-AGGREGATES OF RES CELLS, GRADE 1

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 60
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : D4, 250 MG/KG

FEMALE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 58
DAYS ON TEST : 28

.....
* NECROPSY FINDINGS

KIDNEYS:

IRREGULAR SURFACE.

STOMACH:

LIMITING RIDGE: THICKENED.

ORAL CAVITY:

JAW(S): INCISORS WHITE, OVERGROWTH OF UPPER INCISORS.

OVARIES:

LEFT SIDE: WATERY CYST.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-CHRONIC INTERSTITIAL NEPHRITIS, GRADE 3

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 2

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

OVARIES:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 61
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

FEMALE

* STATE AT NECROPSY: R1 * ANIMAL NO. : 59
DAYS ON TEST : 28

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO MICROSCOPIC FINDINGS NOTED.

* STATE AT NECROPSY: R1 * ANIMAL NO. : 60
DAYS ON TEST : 28

* NECROPSY FINDINGS

ORAL CAVITY:

JAW(S): INCISORS WHITE.

ALL OTHER ORGANS WITHOUT NECROPSY OBSERVATIONS

* MICROSCOPIC FINDINGS

HEART:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

LIVER:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

SPLEEN:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

KIDNEYS:

-CORTICOMEDULLARY MINERALIZATION, MULTIFOCAL, GRADE 1

STOMACH:

-GASTRITIS GLANDULAR STOMACH (MULTI)FOCAL, GRADE 1

ADRENAL GLANDS:

ORGAN EXAMINED, NO PATHOLOGIC FINDINGS NOTED

ORAL CAVITY:

ORGAN NOT EXAMINED

MICROSCOPY NOT APPLICABLE

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

PAGE : 62
TOX NO.: 126282

TEST ARTICLE : TKK 30059 (ZK RT 1507) PATHOL. NO.: 94025 WIM
TEST SYSTEM : RAT, 28-DAY AND REC., ORAL. DATE : 23-DEC-94
SPONSOR : Ciba-Geigy AG PATHDATA SYSTEM V3.5d

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 250 MG/KG

FEMALE

CONT./FF. ANIMAL NO. : 60

END OF REPORT SECTION
LAST PAGE OF REPORT



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Anthony Di Battista
Manager, Regulatory Affairs & Toxic Substances Compliance
Toxicology, Regulatory Auditing & Compliance
CIBA-GEIGY Corporation
444 Saw Mill River Road
Ardsley, New York 10502-2699

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 10 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

13321A



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: APR 19 1995

NON-CAP

CAP

Submission number: 1332/A

TSCA Inventory:

Y

N

D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX ~~SETOX~~ SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 1 2 pages 1,2

pages 1,2,TMB

Notes: 2-sided

Contractor reviewer: P/R

Date: 4/3/95

8 (E) -13321A

H

SUBACUTE ORAL TOXICITY IN WISTAR RATS IS OF HIGH CONCERN BASED ON DAMAGE TO KIDNEYS AT LOW DOSE. DOSAGES (GAVAGE, 5 EACH SEX PER GROUP FOR 28 DAYS) WERE: 0 MG/KG/DAY, 5 MG/KG/DAY, 50 MG/KG/DAY, OR 250 MG/KG/DAY. NO MORTALITIES OCCURRED. DEGENERATION OF RENAL TUBULES WAS OBSERVED AT ALL DOSE LEVELS. IRRITATION OF THE STOMACH AND INCREASED KIDNEY WEIGHT WERE FOUND AT 50 AND 250 MG/KG/DAY. AT 250 MG/KG/DAY ADDITIONAL FINDINGS INCLUDED PILOERCTION; HUNCED POSTURE; ANEMIA; INCREASED LIVER WEIGHT; INCREASED CREATINE, UREA, LIVER ENZYMES, TRIGLYCERIDES AND INORGANIC PHOSPHATES; AND DECREASED GLUCOSE, PROTEIN, AND CHLORIDE LEVELS.